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:	91539 (310723)	NCT00471991
Study Phase:	II	
Official Study Title:	Monocenter, open-label, randomized study to determine the ovulation inhibitory effect of the combined oral contraceptives SH T04769G (0.015 mg Ethinylestradiol and 1.5 mg Dienogest in a modified release medicinal product) and SH D00659AF (0.03 mg Ethinylestradiol and 2.0 mg Dienogest), applied for two treatment cycles to 60 healthy female volunteers	
Therapeutic Area:	Women's Healthcare	
Test Product		
Name of Test Product:	Test product 1: Ethinylestradiol + Dienogest (SH T04769G) Test product 2: Ethinylestradiol + Dienogest (SH D00659AF)	
Name of Active Ingredient:	Ethinylestradiol (EE) + Dienogest (DNG)	
Dose and Mode of Administration:	Test product 1: 0.015 mg EE and 1.5 mg DNG, oral administration Test product 2: 0.03 mg EE and 2.0 mg DNG, oral administration	
Reference Therapy/Placebo		
Reference Therapy:	Not applicable	
Dose and Mode of Administration:	Not applicable	
Duration of Treatment:	Two treatment cycles of 21 days each followed by 7 tablet-free days	
Studied period:	Date of first subjects' first visit:	23 APR 2007
	Date of last subjects' last visit:	03 DEC 2007
Premature Study Suspension / Termination:	No	
Substantial Study Protocol Amendments:	Protocol Amendment no. 1 (dated 18 MAR 2008) was issued after end of the planned subject examinations in the frame of the study. The intention was to collect additional data on the effect of SH D00659AF (0.03 mg EE and 2.0 mg DNG/Test 2) on biosynthesis of steroid hormones and their precursors from the adrenal cortex in fertile women. It was decided to assay the serum levels of dehydroepiandrosterone sulfate (DHEA-S), sex hormone-binding globulin (SHBG), and testosterone using the residual blood samples after completion of the other planned hormone analyses.	
Study Centre(s):	This study was conducted at one center in Germany.	
Methodology:	This was a non-controlled, parallel-group study with 4 cycles (1 pre-treatment cycle, 2 treatment cycles, 1 post-treatment cycle). The pre-treatment cycle started with the first day of bleeding after Visit 1 (Screening). The subjects entered the treatment phase only if the pre-treatment cycle was assessed as ovulatory (i.e., follicular diameter ≥15 mm). During the treatment cycles, frequent measurements of ovarian	

	activity (every 3rd day) were carried out to confirm ovulation or its inhibition. After Treatment cycle 2, ovarian activity was monitored during a post-treatment cycle to assess the return to normal ovarian function. For the pharmacokinetic measurements, blood samples were obtained during pre-treatment cycle on Day 23 and during Treatment cycle 2 on Days 16, 19, 21, and 22. Ovulation inhibition in Treatment cycle 2 was assessed by ultrasonographic monitoring (TVU) of the leading follicle diameter and by analysis of serum hormone levels (estradiol, progesterone). Ovarian activity was classified according to Hoogland and Skouby (1993) (Hoogland HJ and Skouby SO. Ultrasound evaluation of ovarian activity under oral contraceptives. Contraception 1993; 47:583-590). A score of <6 was regarded as inhibition of ovulation.
Indication/ Main Inclusion Criteria:	Indication: Hormonal contraception Main inclusion criteria: Healthy female subjects, aged 18-35 years (smokers only until age of 30 years, inclusive)
Study Objectives:	<u>Overall:</u> The aim of this study was to determine the ovulation inhibitory effect of the combined oral contraceptive (COC) SH T04769G (0.015 mg EE + 1.5 mg DNG in a modified release film-coated tablet) and to collect supplementary data regarding the ovulation inhibitory effect of SH D00659AF (0.03 mg EE + 2.0 mg DNG) in Treatment cycle 2.
Evaluation Criteria:	<u>Efficacy (Primary):</u> • Ovulation inhibition in treatment cycle 2 <u>Efficacy (Secondary):</u> • Grading of ovarian activity according to Hoogland and Skouby (1993) • Follicle size (leading follicle) • Serum levels of estradiol (E2), progesterone, follicle-stimulating hormone (FSH), and luteinizing hormone (LH) • Assessment of cervical mucus according to Insler (1972) • According to amendment no. 1 (dated 18 MAR 2008): Serum levels of DHEA-S, SHBG, and testosterone (only in subjects receiving SH D00659AF) <u>Safety:</u> • Baseline findings and adverse events (AEs) • Safety laboratory tests • Physical and gynecological examination (including vital signs, breast palpation, TVU, and cytological cervical smear) • Cycle control • Pregnancy tests • Prior and concomitant medication

	Pharmacokinetics: In steady state (ss) (only in subjects receiving SH T04769G) • Minimum concentration [$C_{min,ss}$] • Maximum concentration [$C_{max,ss}$] • Time to reach C_{max},ss [$t_{max,ss}$] • Area under the concentration-versus-time curve [AUC(0-24h),$_{ss}$] • Peak-trough fluctuation [PTF]
Statistical Methods:	Efficacy (Primary): For the primary efficacy variable (ovulation inhibition in Treatment cycle 2) and the grading of ovarian activity during the study, both per-protocol set (PPS) and full-analysis set (FAS) analyses were performed. The primary analysis was based on the PPS. Descriptive statistics including one-sided 95% confidence intervals were used. Efficacy (Secondary): For the remaining secondary efficacy variables only the FAS analysis was performed. Descriptive statistics including one-sided 95% confidence intervals were used. Safety: For the safety variables, only the FAS analysis was performed. Descriptive statistics including one-sided 95% confidence intervals were used.
	Pharmacokinetics: Descriptive statistics including one-sided 95% confidence intervals were used.
Number of Subjects:	Planned: 2 treatment groups of 30 Analyzed: FAS: 30 + 30 PPS: 28 + 28

Study Results

Results Summary — Subject Disposition and Baseline

Of 85 screened women requiring contraception, without contraindications for COC use and in good general health, 24 failed to meet the selection criteria, withdrew their consent before study start, were lost before randomization, or were not eligible due to other reasons; 61 subjects were randomized to one of the study treatments. Of them, 1 subject was withdrawn before start of study treatment due to premature follicular ripening (protocol deviation). As a result, 30 subjects received SH T04769G (Test 1) and 30 subjects received SH D00659AF (Test 2); all of them provided data for analysis (FAS). Premature discontinuation of study treatment occurred in 2 subjects from Test 1 group (1 withdrew consent; 1 due to adverse event) and in 1 subject from Test 2 group (1x withdrawal of consent). Correspondingly, 28 subjects in Test 1 group and 29 in Test 2 group completed the study treatment. After analysis of deviations from protocol in individual subjects, 28 subjects in each treatment group were assigned to the PPS (N=56) for analysis of the primary variable. The subjects included in the FAS of this parallel-group study (N=60) had a mean age of 28.6 ± 3.11 years, mean height of 167.9 ± 6.05 cm, mean body weight of 62.07 ± 8.391 kg, and mean body mass index (BMI) of 22.020 ± 2.7273 kg/m^2. All subjects were Caucasian.

Results Summary — Efficacy

The primary efficacy variable of this study was ovulation inhibition during Treatment cycle 2 (no/yes), as assessed by

- Ultrasonographic monitoring (TVU) of leading follicle diameter, and by
- Analysis of serum hormone levels (estradiol, progesterone).

Ovarian activity (assessment based on follicle size and serum levels of estradiol and progesterone) was classified according to Hoogland and Skouby (1993). A Hoogland score of <6 was regarded as inhibition of ovulation. During the cycle before study drug administration (Pre-cycle -1), the grading of ovarian activity demonstrated that 96.4% of the subjects of the PPS assigned to each of both treatments (SH T04769G/Test 1 and SH D00659AF/Test 2) had an ovulatory cycle, i.e., an ovarian activity score of 6. During treatment (Treatment cycle 2), scores of <6 (indicative of non-ovulatory cycle) were seen in 25 of 28 subjects (89.3%) under treatment with Test 1, thus the estimated relative frequency of ovulation inhibition was 0.89 versus 28 of 28 subjects (100%) under treatment with Test 2, thus the estimated relative frequency of ovulation inhibition was 1.0. During a follow-up cycle (Post-cycle) without study treatment, the proportion of subjects with ovulatory cycle was comparable again in both treatment groups with 24 of 28 subjects (85.7%) after Test 1 versus 23 (82.1%) after Test 2.

The relative incidence (lower one-sided 95% CI) of subjects with ovulation inhibition in Treatment cycle 2 in the PPS (primary analysis set) under both study treatments was 0.89 (0.7458303) in the Test 1 group versus 1.0 (0.8985343) in the Test 2 group.

The same was true also for the FAS population because there were no additional data as compared to the PPS (there were 2 subjects in each treatment group without data on the Hoogland score, i.e., missing data were not considered in the calculations).

In conclusion, ovulation inhibition could not be proven for all women treated with SH 04769G. An inhibition of ovulation during Treatment cycle 2 was observed in only 25 of the 28 women in the group treated with the test product SH 04769G (Test 1). This leads to an exact one-sided lower 95% confidence limit of 74.6%. For the test product SH D00659AF (Test 2), this limit was 89.9%, as expected, because ovulation inhibition was observed in all women with data.

During Treatment cycle 2, a noticeable difference in the size of leading follicle was seen between the 2 treatment groups: higher mean diameters of leading follicle ranging between 12.51 ± 9.504 and 13.57 ± 9.147 mm on Days 7 to 19 were seen in Test 1 group as compared to values ranging between 8.80 ± 8.513 and 10.04 ± 8.050 mm in Test 2 group. In contrast to Treatment cycle 2, mean sizes of leading follicles during the Pre-cycle -1 and the Post-cycle were comparable between the two treatment groups.

Since serum levels of estradiol, progesterone, FSH, and LH are indicative of ovarian function, they were regularly assessed.

- Comparison between the 2 treatment groups showed similar mean levels of estradiol during Pre-cycle -1. During the Treatment cycle 2, mean estradiol levels differed most pronounced on Cycle day 7 (0.5679 ± 0.68955 in Test 1 group versus 0.3064 ± 0.71989 in Test 2 group) and on Cycle day 10 (0.6036 ± 0.81815 in Test 1 group versus 0.3831 ± 0.81795 in Test 2 group) which was indicative of a stronger suppression under Test 2. Post-cycle mean estradiol values on Days 7 to 19 appeared to be slightly higher after treatment with Test 2 (0.6414 ± 0.36081 to 0.7362 ± 0.73676 nmol/L) as compared to those after treatment with Test 1

(0.5019 ± 0.31380 to 0.5907 ± 0.34212 nmol/L).

- The characteristic increase of progesterone during the second half of the cycle was seen in the 2 treatment groups reaching comparable levels during the Pre-cycle -1. During Treatment cycle 2, strong suppression of progesterone occurred under both treatments. During Days 19 to 28, mean values ranged between 1.909 ± 0.8162 and 2.129 ± 0.8525 nmol/L in Test 1 group versus values between 1.486 ± 0.6641 and 1.705 ± 0.7036 nmol/L in Test 2 group. Slight dissimilarity in the progesterone suppression was seen at the beginning of Treatment cycle 2 with the most pronounced difference on Day 7 with 3.720 ± 6.9404 in Test 1 group versus 1.651 ± 0.7042 nmol/L in Test 2 group. During Days 19 to 27 of Post-cycle, mean progesterone values ranged from 4.485 ± 2.9628 to 27.231 ± 27.4084 nmol/L after Test 1 versus 8.835 ± 11.1890 to 52.484 ± 37.2127 nmol/L after Test 2.
- Concerning FSH, the 2 treatment groups had comparable mean levels during Days 7 to 19 of the Pre-cycle -1 and the Post-cycle. Secretion of FSH during Days 7 to 19 of Treatment cycle 2 was less suppressed by Test 1 as compared to Test 2 as demonstrated by mean levels ranging between 3.34 ± 2.010 and 4.11 ± 1.997 mU/mL under Test 1 versus 1.59 ± 1.141 and 3.16 ± 1.432 mU/mL.
- The 2 treatment groups displayed comparable mean LH levels during Cycle days 7 to 19 of the Pre-cycle -1 and the Post-cycle. During Cycle days 7 to 19 of Treatment cycle 2, LH secretion was less suppressed under treatment with Test 1 with mean values ranging between 4.05 ± 3.275 and 5.93 ± 3.662 mU/mL as compared to Test 2 with mean values ranging between 1.49 ± 1.241 and 3.76 ± 2.555 mU/mL.

The cyclic changes of cervical mucus in response to the changing patterns of ovarian steroid secretion were regularly monitored during the study treatment. In general, the 2 study treatments produced similar results with regard to the changes of physical and chemical properties of cervical mucus during Treatment cycle 2. Around the days of ovulation (Days 15/16), higher scores (>0) for Amount of mucus, Spinnbarkeit, Ferning, and Appearance of cervical os clearly predominated in their frequency during the Pre-cycle -1 as compared to the frequency of score 0. In contrast, on the same days during Treatment cycle 2, a shift to score 0 became apparent. The frequency of scores of 2 and 3 clearly decreased during Treatment cycle 2 in both treatment groups.

In addition to the main focus on ovulation inhibition parameters of the 2 study drugs, it was intended to obtain additional data on the effect of SH D00659AF (0.03 mg EE + 2.0 mg DNG) on the biosynthesis of steroid hormones and their precursors from the adrenal cortex in fertile women. Serum levels of DHEA-S, SHBG, and testosterone were determined only in subjects receiving SH D00659AF (Test 2).

- Data on serum DHEA-S during Days 7 to 19 of Treatment cycle 2 under Test 2 revealed a slight decrease with mean values ranging between 4.88 ± 2.257 and 5.47 ± 2.472 µmol/L as compared to the levels during Pre-cycle -1 and Post-cycle ranging between 6.08 ± 2.755 and 6.93 ± 3.133 µmol/L.
- As expected, mean levels of SHBG markedly increased during treatment with Test 2 (Days 7 to 19 of Treatment cycle 2) with mean values ranging between 212.98 ± 77.934 and 267.77 ± 71.911 nmol/L as compared to values between 61.29 ± 22.905 and 67.75 ± 23.469 nmol/L during the Pre-cycle -1 and between 88.71 ± 31.769 and 127.82 ± 44.324 nmol/L during the Post-cycle.
- Mean serum levels of testosterone during Days 7 to 19 of treatment with Test 2 (Treatment cycle 2) decreased to values between 0.818 ± 0.6328 and 1.045 ± 0.7752 nmol/L as compared to mean values in the range from 1.398 ± 0.7582 to 1.875 ± 1.9779 nmol/L seen during Pre-cycle -1 and the Post-cycle.

Results Summary — Safety

A total of 170 AEs were reported by 53 subjects of all 60 (88.3%) during this comparative parallel-group study. There were no deaths and no serious AEs (SAEs) during the study. One subject from the Test 1 group was withdrawn from the study due to an AE (Gastrointestinal infection of moderate intensity, non-related to study drug).

A comparable number of subjects experienced AEs under both treatments during the study, namely, 27 subjects of 30 (90.0%) under Test 1 treatment versus 26 of 30 (86.7%) under Test 2 treatment. The number of AEs under the 2 treatments was equal: 85 AEs in each treatment group. This was paralleled by similar proportions of the subjects with AEs rated as drug-related AEs (adverse drug reactions, ADRs): 1 subject in each treatment group with probably related AE, followed by 14 AEs in 11 subjects (36.7%) in Test 1 group with possibly related AEs versus 11 AEs in 8 subjects (26.7%) in Test 2 group.

The following AEs were considered as drug-related to Test 1, namely: Breast discomfort in 4 subjects (13.3%), Breast enlargement, Acne, and Dysmenorrhea in 2 subjects (6.7%) each, Breast pain, Mood altered, Orthostatic intolerance, Elevated mood, and Hot flush in 1 subject (3.3%) each versus drug-related to Test 2, namely: Nausea in 3 subjects (10.0%), Breast pain and Mood altered in 2 subjects (6.7%) each, Breast discomfort, Breast enlargement, Appetite disorder, Headache, and Breast tenderness in 1 subject (3.3%) each.

Nearly two-thirds of the AEs in each treatment group were of mild intensity: 55 AEs in 26 subjects (86.7%) in Test 1 group versus 52 AEs in 21 subjects (70.0%) in Test 2 group.

Only 1 subject in each treatment group experienced an AE of severe intensity. None of these AEs (Migraine without aura under Test 1 and Bartholin's abscess under Test 2) were considered as related to the study drugs or to the study conduct.

Regarding the outcome of AEs, there was only 1 subject (3.3%) in Test 1 group with Eczema who was still recovering at the end of the study; the AE was of mild intensity and considered non-related to the study drug. All other AEs in both treatment groups were assessed as recovered. There were no AEs that were not recovered/not resolved.

Safety laboratory parameters stayed generally stable during the study and no marked changes were seen. No laboratory values outside the normal ranges were seen in Sodium, Potassium, Creatinine, Albumin, Gamma-glutamyl transferase (GT) (in both treatment groups). There were no laboratory values reaching the alert range during the treatment and the post-treatment cycles. Single or few values (slightly increased or decreased) were seen in Erythrocytes, Leukocytes, Hematocrit, Cholinesterase, high-density lipoprotein (HDL)- and low-density lipoprotein (LDL)-cholesterol, and Hemoglobin A1C. Laboratory values outside normal range (at Final examination) were seen slightly more frequently in Hemoglobin (decreased: 7 under Test 1 versus 6 under Test 2), Total protein (decreased: 2 under Test 1 versus 6 under Test 2), Alkaline phosphatase (decreased: 5 under Test 1 versus 1 under Test 2), Triglycerides (decreased: 4 in each treatment group; increased: 3 under Test 1 versus 4 under Test 2), and Total cholesterol (decreased: 5 under Test 1 versus 4 under Test 2; increased: 1 under Test 2).

All other safety observations of the study drugs did not provide any reasons for concern. Data on cycle control were generally comparable for both oral contraceptives (OCs). Withdrawal bleeding was predominantly of light and normal intensity in the 2 treatment groups. Only isolated cases reported withdrawal bleeding of heavy intensity. Intracyclic bleeding (mainly spotting and light) occurred rarely during Treatment cycle 2 in both treatment groups with a

slightly higher frequency in Test 1 group, namely 7 subjects (25.0%) versus 4 (13.3%) in Test 2 group. The same tendency was seen also during Treatment cycle 1 with 17 subjects (58.6%) under Test 1 versus 9 (30.0%) under Test 2.

Results Summary — Pharmacokinetics

Evaluation of pharmacokinetic parameters of DNG and EE during steady state after daily oral administration of 1.5 mg DNG and 0.015 mg EE (SH T04769G/Test 1) are summarized in Table 1.

Table 1: Mean pharmacokinetic parameters of DNG and EE during steady state (Treatment cycle 2) after daily oral administration of 1.5 mg DNG and 0.015 mg EE (SH T04769G)

Parameter	C_{max}	C_{min}	t_{max}	AUC(0-24)	PTF
	Geometric mean (CV)	Geometric mean (CV)	Median (range)	Geometric mean (CV)	Geometric mean (CV)
DNG	54.0 ng/mL (15.6%)	7.00 ng/mL (47.6%)	2 h (0.47 - 5.97 h)	575 ng·h/mL (22.5%)	195% (20.8%)
EE	62.3 pg/mL (32.7%)	8.50 pg/mL (47.0%)	1.04 h (0.5 - 2.05 h)	517 pg·h/mL (31.5%)	248% (26.2%)

C_{max} = maximum serum concentration
C_{min} = mininum serum concentration during the dosing interval
t_{max} = time to reach Cmax
AUC(0-24) = area under the serum concentration-time curve from administration to 24h after dosing
PTF = peak-trough-fluctuation
CV = coefficient of variation

Individual serum concentration-time profiles for DNG and EE at steady state at the end of Treatment cycle 2, respectively, are presented in Figures 1 and 2. Subjects indicating signs of ovulation during the entire course of the study are identifiable by symbols. Since the majority of these subjects scatter within the exposure range observed for the remaining subjects, a reduced systemic exposure in these subjects seems not to be directly responsible for the incomplete ovulation inhibition following treatment with SH T04769G.

Figure 1: Superimposed individual concentration-time curves of Dienogest after oral administration of 1.5 mg DNG and 0.015 mg EE (SH T04769G) at steady state during Treatment cycle 2

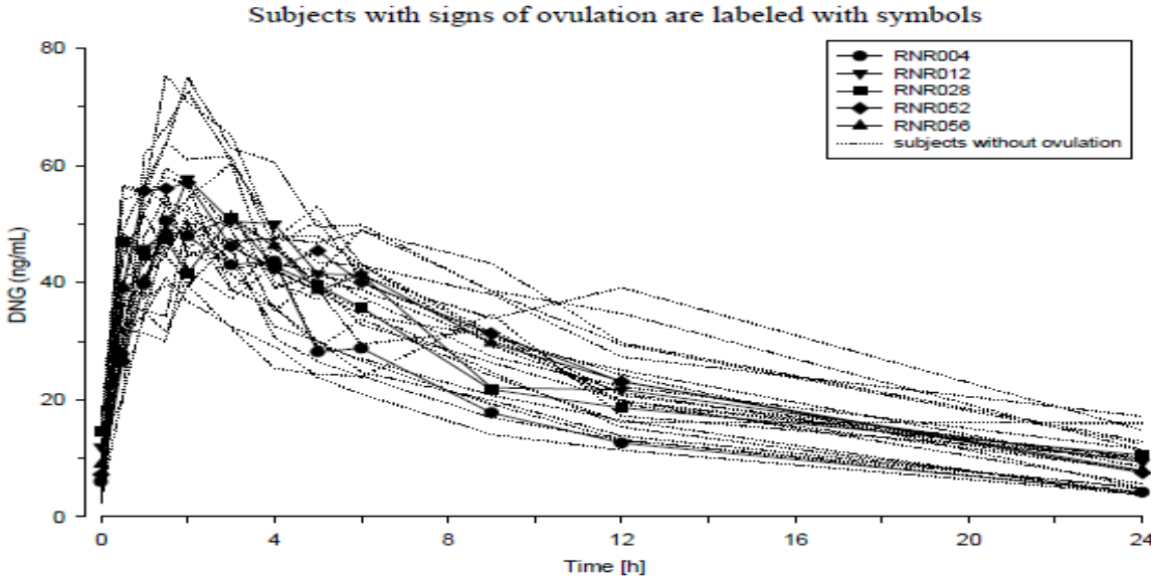
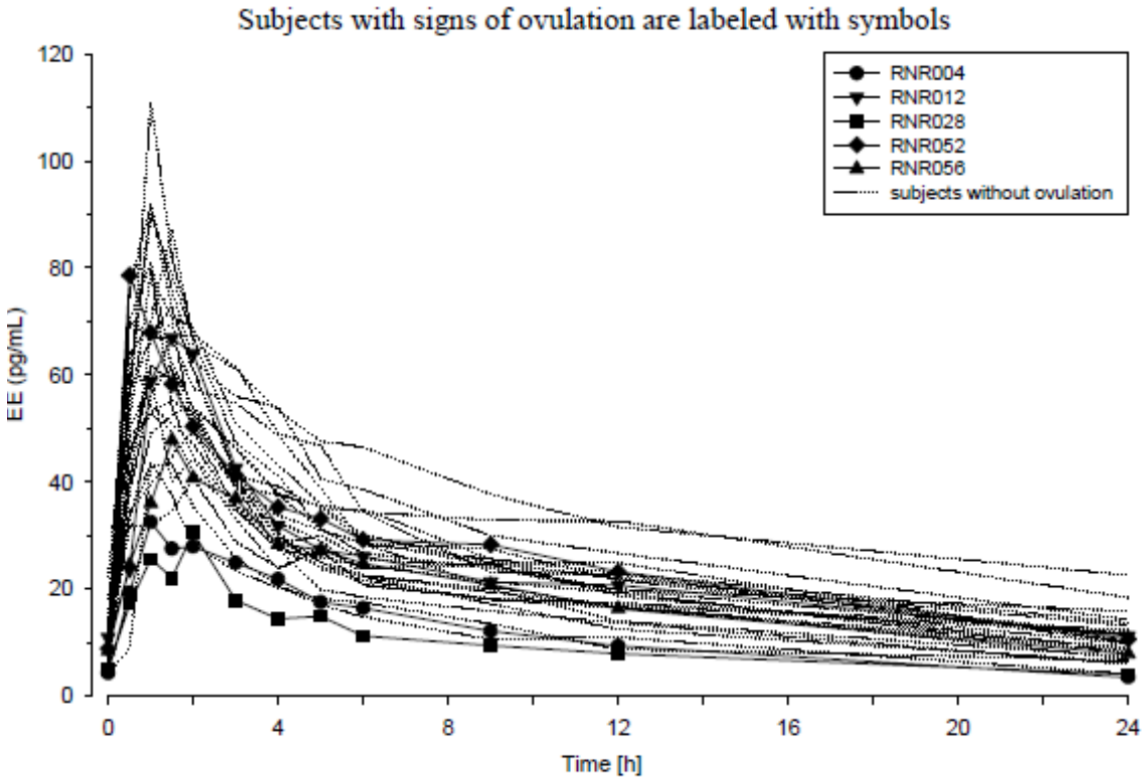


Figure 2: Superimposed individual concentration-time curves of EE after oral administration of 1.5 mg DNG and 0.015 mg EE (SH T04769G) at steady state during Treatment cycle 2



Conclusion(s)

In summary, the modified-release, low-dose formulation Test 1 demonstrated lower efficacy in ovulation inhibition and general suppression of the gonadal axis, most probably due to the reduced dose of the progestin component DNG supported, however, by a very low dose of the estrogen component EE as well. The safety profile also suggests that this dose of DNG insufficiently counteracts the effects of the reduced estrogen dose in this formulation.

Publication(s):	None		
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Investigational Site List

Marketing Authorization Holder in Germany	
Name	Jenapharm GmbH & Co KG
Postal Address	Otto-Schott-Strasse 15 07745 Jena Germany
Sponsor in Germany	
Legal Entity Name	Bayer HealthCare AG
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