Clinical Study Synopsis

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Bayer HealthCare

Clinical Trial Results Synopsis

Study Design Description		
Study Sponsor:	Bayer HealthCare AG	
Study Number:	91587 (310882)	NCT00569244
Study Phase:	III	
Official Study Title:	A multi-center, open-label, randomized, controlled, parallel-group study to assess efficacy and safety of an extended flexible regimen of the combined oral contraceptive SH T00186D (0.02 mg ethinylestradiol as beta-cyclodextrin clathrate and 3 mg drospirenone) compared to the conventional regimen of SH T00186D in the treatment of primary dysmenorrhea	
Therapeutic Area:	Women's Healthcare	
Test Product		
Name of Test Product:	EE20/DRSP (YAZ, BAY86-5300)	
Name of Active Ingredient:	Ethinylestradiol (EE), Drospirenone (DRSP)	
Dose and Mode of Administration:	EE (as beta-cyclodextrin clathrate): 0.02 mg + DRSP: 3 mg (Yaz flexible), Oral administration	
Reference Therapy/Placebo		
Reference Therapy:	EE/DRSP [SH T00186DF/Conventional regimen (Yaz conventional)]	
Dose and Mode of Administration:	EE (as beta-cyclodextrin clathrate): 0.02 mg + DRSP: 3 mg, Oral administration	
Duration of Treatment:	For Test product: Intended consecutive daily intake for 120 days followed by a 4-day tablet-free interval. In case of unscheduled bleeding of at least 3 consecutive days, a 4-day tablet-free interval was advised. This was to start at the earliest on the 4th day of bleeding. Treatment started after any tablet-free interval (i.e., planned after 120 days of consecutive intake or due to unscheduled bleeding) had to have a duration of at least 24 days (1 blister pack). Treatment was to last at least 140 days. Prolonged treatment was potentially possible due to variation in cycle length with the extended flexible regimen. For Reference therapy: 5 cycles, each consisting of 28 days, resulting in 140 days of consecutive intake Cycle days 1 – 24: 0.02 mg EE + 3 mg DRSP Cycle days 25 – 28: Placebo	
Studied period:	Date of first subjects' first visit:	07 DEC 2007
	Date of last subjects' last visit:	01 DEC 2009
Premature Study Suspension / Termination:	No	
Substantial Study Protocol Amendments:	Amendment no. 1 (dated 22 MAY 2008) specified the following changes:	

	• The number of study centers planned changed from 35 in Germany to 30 centers in Germany + 4 centers in the UK. • Ibuprofen as rescue medication came from another manufacturer with a product marketed in the UK.
Study Centre(s):	The number of active centers was 26 in Germany and 3 in the United Kingdom.
Methodology:	In this multicenter, open-label, randomized, controlled, parallel group study, two groups of subjects were distinguished at screening regarding their history of oral contraceptive use: switchers from another oral contraceptive (OC) (eligible subjects had to undergo 3 washout cycles) and OC starters (no washout period was required). Treatment was initiated after the two baseline cycles. Only subjects who experienced a sum score of ≥8 (sum pain score means that the daily dysmenorrhea scores were summed up during the 2 baseline cycles.) during the two baseline menstruations were randomized. After end of the treatment period, a 4-day tablet-free interval was required before starting a post-study contraceptive method again. Subjects were required to fill out their diary cards regularly. Data for the number of days with dysmenorrheic pain during 140 days of treatment was collected using daily records on the diary cards. Pain was self-assessed by a categorical pain scale on a daily basis by the subjects. The documentation started immediately after Visit 1 and continued until final visit or at least until 2 days after the last day of the withdrawal bleeding that followed the treatment period. In case of premature discontinuation, the diary was to be filled out at least until 2 days after the end of the withdrawal bleeding that followed the premature end of treatment.
Indication/ Main Inclusion Criteria:	Indication: Primary dysmenorrhea Inclusion criteria: Otherwise healthy female subjects with moderate to severe primary dysmenorrhea (present in at least 4 out of 6 preceding cycles), as defined below: • Moderate dysmenorrhea: Need for over-the-counter (OTC) analgesics during menstruation, significant pain relief upon intake, interference with usual activities. • Severe dysmenorrhea: Need for analgesics during menstruation, OTC analgesics not consistently effective, prescription analgesics required in at least some cycles, discomfort causes inability to work or to do usual activities. • Prospective self-rated sum pain score of ≥8 during the 2 baseline menstrual cycles (dysmenorrhea grading according to Andersch and Milsom, 1982 [Andersch B, Milsom I. An epidemiologic study of young women with dysmenorrhea. Am J Obstet Gynecol 1982, 144(6):655-60]). • Age between 18 and 40 years (inclusive) with smoking habits as follows: ➢ Between 18 and 30 years of age, daily cigarette consumption not above 10, ➢ Above 30 years of age, no smoking.

Study Objectives:	Overall: To investigate the efficacy and safety of SH T 00186D in an extended flexible regimen compared to the conventional cycle regimen (24 + 4 days) in 216 female subjects aged between 18 and 40 years (smokers at a maximum age of 30 years, inclusive) suffering from moderate to severe primary dysmenorrhea. Primary: The primary objective of the study was to evaluate the antidysmenorrheic effects of the COC BAY86-5300 (0.02 mg ethinylestradiol [EE] and 3 mg drospirenone [DRSP]) applied in an extended flexible regimen compared to BAY86-5300 in a conventional regimen (24 + 4 days). The primary target variable was the number of days with dysmenorrheic pain during 140 days of treatment. Secondary: Rescue medication intake, interference with daily activity, number of days with at least moderate dysmenorrheic pain, number of days with pain (independent of occurrence of vaginal bleeding), number of days with dysmenorrheic pain associated with withdrawal bleeding, number of days with dysmenorrheic pain associated with unscheduled bleeding, bleeding patterns, and investigator assessment of overall improvement of primary dysmenorrhea by means of Clinical Global Impression (CGI) scale were secondary efficacy variables. A subjective assessment of treatment was required.
Evaluation Criteria:	Efficacy (Primary): • Number of days with dysmenorrheic pain over 140 days of treatment. Efficacy (Secondary): • Number of days with at least moderate dysmenorrheic pain over 140 days of treatment, • Number of days with pelvic pain (independent of occurrence of vaginal bleeding) over 140 days of treatment, • Number of days with dysmenorrheic pain associated with withdrawal bleedings over 140 days of treatment, • Number of days with dysmenorrheic pain associated with unscheduled bleedings over 140 days of treatment, • Use of rescue medication (standardized intake of ibuprofen), • Interference with daily activity, • Bleeding patterns, • Investigator assessment of total improvement of primary dysmenorrhea by Clinical Global Impression (CGI) rating scale, • Subjective assessment of treatment by the subject. Safety: • Baseline findings and adverse events (AE), • Safety laboratory tests, • Pregnancy tests, • Physical and gynecological examination (including vital signs, breast palpation, transvaginal ultrasonography [TVU], and cytological cervical smear), • Prior and concomitant medications.

Statistical Methods:	Efficacy (Primary): Testing of treatment differences in dysmenorrheic pain, using t-tests, 2-sided 95% confidence interval (CI) and a 2-sided level of significance of alpha = 0.05 . No interim analysis was done. Efficacy (Secondary): Two-sided 95% confidence intervals were calculated for the secondary variables. Safety: Safety variables were analyzed by descriptive statistics.
Number of Subjects:	Planned: Sample size per group: 108/Total sample size: 216 Analyzed: Group A (extended flexible regimen = Yaz flexible): Full-analysis set (FAS) = 115; Per-protocol set (PPS) = 92 Group B (conventional cycle regimen = Yaz conventional): FAS = 108; PPS = 100

Study Results

Results Summary — Subject Disposition and Baseline

Screening of 272 subjects with moderate to severe primary dysmenorrhea resulted in classification of 41 subjects (15.1%) as screening failures and 231 subjects (84.9%) as eligible for the study. A total of 231 subjects were randomized to one of the 2 treatment regimens Yaz flexible (Group A) and Yaz conventional (Group B). Number of randomized subjects who either did not take the study medication (3 subjects "study medication never administered") or their study medication status remained unknown (5 subjects "no information available"). Finally, there were 223 subjects [FAS = 100.0%] who started taking the study medication: 115 subjects (100.0%) in Group A and 108 (100.0%) in Group B. Study medication was completed as planned by 210 subjects (94.2%), i.e., 110 (95.7%) in Group A and 100 (92.6%) in Group B. There were 13 subjects (5.8%) who prematurely discontinued the study medication: 5 (4.3%) in Group A and 8 (7.4%) in Group B.

The following reasons for premature discontinuation were reported:

- Adverse event(s) reported by 5 subjects (2.2%),
- Withdrawal of consent by 3 subjects (1.3%),
- Protocol deviation in 2 subjects (0.9%),
- "Other" for 2 subjects (0.9%) (1x subject's mistake, 1x elective cosmetic surgery) and
- Pregnancy in 1 subject (0.4%).

The mean age of the subject sample was 25.5 ± 5.0 years (median age was 25.0 years). The majority of subjects, 215 of 223 (96.4%), were Caucasian and the other 8 subjects were of the following origin: 5 subjects were of Asian origin, 2 subjects were classified as Black, and 1 subject specified as Arabic. The overall mean height was 167.91 ± 6.28 cm (median 168.00 cm); mean body weight was 63.40 ± 9.30 kg (median 62.00 kg). Mean body mass index (BMI) was 22.476 ± 2.967 kg/m^2 (median BMI was 22.030 kg/m^2). The majority of subjects, 208 (93.3%) reported to be sexually active. Less than one third of the subjects, 67 (30.0%), reported to smoke. A high number of subjects, namely 160 (71.7%), reported seldom alcohol consumption, followed by 37 subjects (16.6%) who stated to never consume alcohol, and 26 subjects with occasional alcohol consumption (11.7%). The treatment groups were well-matched in terms of the above described basic characteristics.

The subjects in both treatment groups displayed good treatment compliance. Mean number of Yaz tablets taken was 151.8 ± 31.8 (median: 146.0) in Group A (extended flexible regimen) versus 135.6 ± 26.0 (median: 140.0) in Group B (conventional regimen).

Dysmenorrheic pain: The primary target variable was the number of days with dysmenorrheic pain over 140 days of treatment. The treatment with SH T00186D (Yaz) in an extended flexible regimen (Yaz flexible) resulted in a significantly lower number of days with dysmenorrheic pain compared to the conventional regimen (Yaz conventional). The benefit of the Yaz flexible regimen was confirmed by the results of the analysis of the secondary variables. The number of days with at least moderate dysmenorrheic pain as well as the number of days with pelvic pain (independent of occurrence of vaginal bleeding), the number of days with dysmenorrheic pain associated with withdrawal bleeding, and the number of days with interference of pain with daily activity were lower in the group with the Yaz flexible regimen compared to those with the Yaz conventional regimen as summarized in Table 1. The number of days with dysmenorrheic pain associated with unscheduled bleeding and the number of days with use of rescue medication were comparable in both treatment groups.

Table 1: Number of days with at least moderate dysmenorrheic pain as well as the number of days with pelvic pain (independent of occurrence of vaginal bleeding), the number of days with dysmenorrheic pain associated with withdrawal bleeding, and the number of days with interference of pain with daily activity over 140 treatment days

Parameter (over 140 treatment days) **Days with:**	**Yaz flexible** mean ± SD (n)	**Yaz conventional** mean ± SD (n)	**Treatment difference in days**	**95% confidence interval**
dysmenorrheic pain	10.6 ± 7.8 (112)	14.9± 8.9 (102)	-4.2 (p=0.0003)	(-6.5, -2.0)
at least moderate dysmenorrheic pain	4.0 ± 3.1 (112)	6.5 ± 5.3 (102)	-2.5	(-3.7, -1.3)
pelvic pain	12.2 ± 9.1 (112)	15.6 ± 9.5 (102)	-3.4	(-5.9, -0.9)
dysmenorrheic pain associated with withdrawal bleeding	5.2 ± 6.3 (112)	9.3 ± 6.5 (102)	-4.1	(-5.8, -2.4)
dysmenorrheic pain associated with unscheduled bleeding	5.4 ± 4.3 (112)	5.5 ± 4.4 (102)	-0.1	(-1.3, 1.0)
use of rescue medication	4.7 ± 5.1 (112)	5.7 ± 6.0 (102)	-1.0	(-2.5, 0.5)
interference with daily activities	6.9 ± 7.0 (112)	9.0 ± 8.3 (102)	-2.2	(-4.2, -0.1)

Bleeding pattern: Using the 90-day reference period method, analysis of the number of bleeding/spotting days during the two reference periods revealed slight differences between the 2 treatment regimens. Lower mean and median numbers of bleeding/spotting days were seen during treatment with the Yaz flexible regimen as compared to those with the Yaz conventional regimen [e.g., 19.9 ± 13.0 (17.0) days in Group A versus 25.3 ± 9.1 (23.0) days in Group B during the first 90-day period]. Note the higher variability of data with the Yaz flexible regimen. The difference shrank slightly during the second 90-day period. The numbers of bleeding/spotting episodes were also slightly lower during treatment with the Yaz flexible regimen as compared to those with the Yaz conventional regimen [e.g., 2.4 ± 1.7 (2.0) episodes in Group A versus 3.5 ± 1.0 (3.0) episodes in Group B during the first 90-day period]. This difference was smaller during the second reference period associated with equal median values of 3.0 in both treatment groups. A higher mean length of bleeding/spotting

episodes in the Yaz flexible Group A during the first 90-day period was associated with a much higher variability, namely: 7.75 ± 9.03 days in Group A versus 5.24 ± 1.83 days in Group B. The median value of length of bleeding/spotting episodes was slightly higher in Group A (6.42 days in Group A versus 5.00 in Group B). In parallel to the mean length, also the mean and median values of the maximum length of bleeding/spotting episodes were higher with the Yaz flexible regimen [10.2 ± 9.7 (median: 9.0) days in Group A as compared to 7.5 ± 3.7 (median: 6.0) days in Group B during the first reference period]. The differences between the groups regarding mean and maximum length of bleeding/spotting episodes almost disappeared during the second period. The range of length of bleeding/spotting episodes was characterized in both treatment groups by high variability of data. In general, mean and median values of the range of length of bleeding/spotting episodes were similar between the 2 treatment regimens.

The analysis of bleeding pattern using the 120-day reference period revealed analogous trends to those seen in the analysis using the 90-day reference period.

Cycle control: Regarding the occurrence of withdrawal bleeding, both treatment regimens displayed comparable proportions of subjects during the 5 treatment cycles; the proportion of subjects with withdrawal bleeding ranged from 85.9% to 96.5% in the Yaz flexible Group A versus 87.0% to 98.0% in the Yaz conventional Group B. The decreasing number of subjects in Group A who experienced 3, 4, or 5 cycles during the study period is explained by the extended flexible regimen itself, i.e., the prolonged active treatment of the extended regimen in contrast to the 24-day active treatment followed by 4-day interval (placebo) of the conventional regimen led to fewer withdrawal bleeding episodes in total. Mean and median length of withdrawal bleeding episodes tended to be higher in the Yaz flexible Group A with values ranging between 6.0 ± 2.6 (median: 5.0) and 9.6 ± 7.4 (median: 8.0) days during the individual treatment cycles as compared to values ranging between 4.9 ± 1.8 and 5.5 ± 2.8 (median: 5.0) days in the Yaz conventional Group B. The longer episodes in the Yaz flexible Group A can be easily explained by the rules of the regimen. Such episodes included by definition the 3 preceding days of spotting/bleeding that the woman was advised to allow before having the 4-day tablet-free interval that initiates the withdrawal bleeding. The 2 treatment regimens were associated with very similar maximum intensities of the withdrawal bleeding episodes with a median value of 4 and a range of 2 – 5; mean values ranged between 3.7 ± 0.9 and 4.0 ± 0.8 in Yaz flexible Group A versus 3.9 ± 0.8 and 4.0 ± 0.8 in Yaz conventional Group B. The descriptive statistics for the onset of withdrawal bleeding differed substantially by definition among the 2 regimens; for example, during Cycle 1: -3.9 ± 7.5 days in the Yaz flexible Group A versus 3.2 ± 4.7 days in the Yaz conventional Group B and during Cycle 2: -0.7 ± 4.3 days in the Yaz flexible Group A versus 3.1 ± 3.9 days in the Yaz conventional Group B. The difference was reflected also in the median values, for example: -3.0 and -2.0 days in the Yaz flexible Group A during the first 2 treatment cycles versus 2.0 and 3.0 days in the Yaz conventional Group B. The proportions of subjects with light and moderate intensities of the withdrawal bleeding episodes were generally comparable between the 2 treatment groups. Slightly lower frequency of heavy withdrawal bleeding episodes was seen in the Yaz flexible Group A; for example, during Cycle 1: 21.8% in Group A versus 29.8% in Group B and during Cycle 2: 21.8% in Group A versus 27.3% in Group B. Moreover, the proportion of subjects with withdrawal bleeding episodes with a maximal intensity "spotting" was slightly higher in the Yaz flexible Group A as compared to the Yaz conventional Group B; for example, during Cycle 1: 13.6% in Group A versus 6.4% in Group B and during Cycle 2: 13.6% in Group A versus 8.1% in Group B.

The two treatment regimens differed markedly with regard to the occurrence of intracyclic bleeding. The difference in the first cycle can be partly explained by different handling of the days with menstrual bleeding at the start of study treatment (women were instructed to start treatment on the first day of menstrual bleeding). While these bleeding days were excluded in the evaluation of the conventional regimen (Group B), they were included in the evaluation of the flexible regimen (Group A). Therefore there is a large difference in intracyclic bleeding

rates between the first cycle and subsequent cycles for women in the Yaz flexible Group A, as well as a large difference in the first cycle between the flexible regimen compared with the conventional regimen of Yaz. In particular, 109 subjects (95.6%) in Group A experienced intracyclic bleeding during treatment Cycle 1, followed by 30 (30.3%) during Cycle 2, and 13 (27.7%) during Cycle 3. The proportions of subjects with intracyclic bleeding in the Yaz conventional Group B varied within a narrow range between 24 (22.2%) (Cycle 1) and 10 (10.0%) (Cycle 4). The two regimens differed also with respect to the number of intracyclic bleeding episodes per treatment cycle. The mean numbers of intracyclic bleeding episodes during the individual 28-day treatment cycles with the Yaz conventional regimen ranged between 0.1 ± 0.3 (Cycle 4) and 0.3 ± 0.6 (Cycle 1). In contrast, there were mean numbers of intracyclic bleeding episodes as high as 1.9 ± 1.8 (Cycle 1) and 1.1 ± 1.6 (Cycle 5) and as low as 0.0 ± 0.2 (Cycle 4) during the extended treatment cycles with the Yaz flexible regimen. The median number of intracyclic bleeding episodes during treatment Cycle 1 in the Yaz flexible Group A was 1 within a range of 0 to 16 episodes. The median number of intracyclic bleeding episodes decreased to 0.0 during the following 3 cycles and 0.5 during Cycle 5; the maximal values decreased also from 16 to 1. Mean maximum length of the intracyclic bleeding episodes during treatment Cycle 1 were comparable between the two treatment regimens: 7.2 ± 7.5 days in Yaz flexible Group A versus 7.1 ± 5.6 in Yaz conventional Group B. A median value of 6.0 days in Group A was higher than 4.5 days in Group B. Note, however, that the number of subjects with intracyclic bleeding with the regimen Yaz flexible was with 109 markedly higher than 24 subjects with intracyclic bleeding with the regimen Yaz conventional. During the following cycles, the number of subjects with intracyclic bleeding clearly decreased; also the mean maximum length of intracyclic bleeding episodes decreased within the 2 treatment groups.

For the differences under continued treatment, it should be noted that while the cycle duration with the conventional regimen was normally 28 days, the individual durations of cycles with the flexible regimen could differ, according to the rules described in the Study Protocol, within a very broad range from 28 up to 124 days (the latter in ideal case). These rules may explain some of the differences observed. The Yaz flexible regimen was designed to achieve prolonged bleeding-free intervals. While bleeding episodes of less than 3 days were to be ignored, episodes of 3 and more days were indicated to be "treated" by introducing a 4-days tablet-free interval, thus converting them into withdrawal bleeding episodes. Not treating shorter bleeding episodes is considered a suitable strategy to avoid too frequent withdrawal bleeding episodes; however, this certainly adds to the incidence of intracyclic bleeding.

The mean number of intracyclic bleeding days during Cycle 1 was noticeably higher in the Yaz flexible Group A [9.3 ± 9.2 (7.0)] as compared to that of the Yaz conventional Group B [1.7 ± 4.3 (0.0)], as could be expected for the considerably longer treatment cycle with the flexible regimen. Mean number of intracyclic bleeding days decreased in both treatment groups during the subsequent cycles; the decrease was more pronounced in the Yaz flexible Group. The median numbers of intracyclic bleeding days were 0.0 in the 2 treatment groups during Cycles 2 to 4. The mean maximum intensity of intracyclic bleeding episodes was comparable between the 2 treatment groups during treatment Cycles 2 to 5. A marked difference was seen during Cycle 1: 4.5 ± 0.6 (median: 5.0) in the Yaz flexible Group A versus 2.7 ± 1.0 (median: 2.0) in the Yaz conventional Group B. With respect to proportions of subjects with different maximum intensity of intracyclic bleeding episodes, there were only few subjects (1 to 3) with intracyclic bleeding episodes of heavy intensity in both treatment groups during treatment Cycles 2 to 5: their proportions ranged from 0 to 20.0% in the Yaz flexible Group A versus 0 to 16.7% in the Yaz conventional Group B. The proportion of spotting and light bleeding episodes clearly predominated in both treatment regimens during Cycles 2 to 5. A pronounced difference between the 2 treatment regimens regarding maximum intensity of intracyclic bleeding was seen during Cycle 1. While only 3 of 109 subjects (2.7%) with the Yaz flexible regimen characterized the maximum intensity of intracyclic bleeding as spotting or light, there were 18 of 24 subjects (75.0%) with the Yaz

conventional regimen with spotting or light intensity of intracyclic bleeding. In contrast, heavy intracyclic bleeding occurred in 62 subjects (56.9%) in the Yaz flexible Group A versus only 2 subjects (8.3%) in the Yaz conventional Group B.

Investigator's assessment of degree of improvement of primary dysmenorrhea: The Global improvement/change item (CGIC) as part of the validated CGI rating scale was applied for this assessment after a clinical interview with the subject and after evaluation of the results of the final examinations. Data analysis displayed a globally "very much" and "much" improved status of dysmenorrhea in 100 subjects (87.0%) in the Yaz flexible Group A versus 83 subjects (76.8%) in the Yaz conventional Group B. "Minimally improved" or "unchanged" status was seen in 12 subjects (10.4%) in Group A versus 20 subjects (18.5%) in Group B. The frequency of subjects with worsened dysmenorrhea ("minimally", "much", and "very much" worse) remained generally very low in both treatment groups: 3 (2.6%) in Group A versus 5 (4.7%) in Group B.

Subjective assessment of treatment by the subject: At the end of treatment, each subject was asked to rate her satisfaction with the study treatment. The frequency analysis revealed that approximately 3/4 of the subjects in each of the 2 treatment groups were "very much" and "much" satisfied with the treatment; approximately 15% in each group reported to be "minimally" satisfied or "neither satisfied/nor dissatisfied"; any dissatisfaction ("minimally", "much", or "very much") was expressed by 7 subjects (6.1%) in the Yaz flexible Group A versus 12 subjects (11.1%) in the Yaz conventional Group B.

Results Summary — Safety

Adverse events: A total of 82 of 223 subjects (36.8%) reported at least 1 AE during the study. The frequency of subjects with AEs was similar in the 2 treatment groups: 44 (38.3%) subjects in Group A with 75 AEs versus 38 (35.2%) subjects in Group B with 70 AEs; a total of 145 AEs were recorded. There were no deaths and no serious AEs. The study drug was withdrawn due to AEs in 5 cases (2.2%): 2 subjects (1.7%) in Group A and 3 subjects (2.8%) in Group B. The following AEs were the reasons for study drug withdrawal: Headache in 1 subject (0.4%), Breast pain in 2 subjects (0.9%), and Metrorrhagia in 2 subjects (0.9%). There were 44 subjects (19.7%) with 1 AE, 23 (10.3%) with 2 AEs, 8 (3.6%) with 3 AEs, 5 (2.2%) with 4 AEs, 1 (0.4%) with 5 AEs, and 1 (0.4%) with 6 AEs. The most frequent AEs (in >1% of the total sample) were as follows (by Medical Dictionary for Regulatory Activities [MedDRA] preferred term, MedDRA Version 12.1): Headache in 12 subjects (5.4%), Nasopharyngitis in 12 subjects (5.4%), Breast pain in 7 subjects (3.1%), Vaginal infection in 7 subjects (3.1%), Diarrhea in 6 subjects (2.7%), Vomiting in 6 subjects (2.7%), Cystitis in 5 subjects (2.2%), Acne in 4 subjects (1.8%), Back pain in 4 subjects (1.8%), Sinusitis in 3 subjects (1.3%), and Vaginitis bacterial in 3 subjects (1.3%).

Characteristics of AEs: The maximal intensity of AEs was mild in 23 subjects (10.3%), moderate in 55 subjects (24.7%), and severe in 2 subjects (0.9%). The distribution of AEs of mild and severe maximum intensity among the 2 treatment regimens was relatively balanced. A slightly higher proportion of subjects with AEs of moderate intensity were seen in Group A (27.8%) versus those in Group B (21.3%). AEs of severe intensity occurred on single occasions in the 2 treatment groups. The following AEs of severe intensity were reported: Toothache (Group A) and Glossitis (Group B). Both AEs were non-serious and were considered non-related to the study drug; the subjects recovered. The main pattern of AE course was continuous in 73 subjects (32.7%) and intermittent in 7 subjects (3.1%). The most relevant study drug action due to AE was "dose not changed" in 65 subjects (29.1%). Specific drug treatment prescribed for the AEs in 57 subjects (25.6%) was distributed as follows: 32 subjects (27.8%) in Group A versus 25 (23.1%) in Group B. No specific drug treatment was recorded for the AEs in 25 subjects (11.2%). Specific non-drug treatment was prescribed for AEs in 7 subjects (3.1%); 75 subjects (33.6%) with AEs did not receive any non-drug treatment.

Causal relationship of AEs and outcome of AEs: The relationship to the study drug for the individual AEs was assessed as follows: AEs in 24 subjects (10.8%) were assessed as related and AEs in 58 subjects (26.0%) as non-related to the study drug. The distribution between the 2 treatment groups was as follows: 12 subjects (10.4%) in Group A experienced drug-related AEs versus 12 subjects (11.1%) in Group B. More frequent drug-related AEs (in ≥1 subject) were: Breast pain in 7 subjects (3.1%), Headache in 5 subjects (2.2%), Metrorrhagia in 2 subjects (0.9%), Acne in 2 subjects (0.9%), Vaginal infection in 2 subjects (0.9%). AEs of the following SOCs were rated as related to the study drug:

- Reproductive system and breast disorders in 10 subjects (4.5%) [Breast enlargement in 1 subject (0.4%), Breast pain in 7 subjects (3.1%), and Metrorrhagia in 2 subjects (0.9%)],
- Nervous system disorders in 5 subjects (2.2%) [Headache in 5 subjects (2.2%) and Migraine in 1 subject (0.4%)],
- Skin and subcutaneous tissue disorders in 3 subjects (1.3%) [Acne in 2 subjects (0.9%) and Skin disorder in 1 subject (0.4%)],
- Eye disorders in 2 subjects (0.9%) [Contact lens intolerance in 1 subject (0.4%) and Photopsia in 1 subject (0.4%)],
- Infections and infestations in 2 subjects (0.9%) [Vaginal infection in 2 subjects (0.9%)],
- Psychiatric disorders in 2 subjects (0.9%) [Apathy in 1 subject (0.4%) and Libido decreased in 1 subject (0.4%)],
- Musculoskeletal and connective tissue disorders in 1 subject (0.4%) [Muscle spasms in 1 subject (0.4%)].

There was a single AE with a causal relationship to the study conduct. The AE Gastroenteritis (Group A) was rated as related to the study conduct (it was a non-serious AE with moderate intensity; the subject recovered). The outcome of the large majority of AEs was "recovered/resolved", namely for 142 AEs in 81 subjects (36.3%); "recovering/resolving" was for 1 AE in 1 subject (0.4%) and "not recovered/not resolved" at the time of database closure remained for 2 AEs in 2 subjects (0.9%). The following 2 AEs (both in subjects in Group B) remained "not recovered/not resolved": Breast enlargement (non-serious, mild intensity, related to study drug) and Headache (non-serious, moderate intensity, drug-related); "recovering/resolving" was the AE Synovial cyst (Group A; non-serious, mild intensity, non-related to study drug).

Clinical laboratory parameters of carbohydrate metabolism, serum chemistry, liver enzymes, serum lipids, and hematology displayed normal mean and median values in both treatment groups at the individual examination times during this study with a treatment duration of approximately 140 days. Only small numbers of abnormal values in most of the laboratory parameters (with the exception of 2 serum lipid parameters) were seen with both treatment regimens; in addition, the frequencies of abnormal values at screening and final examination were generally comparable. More frequent abnormal values were seen in total cholesterol and triglycerides. Like in the other parameters, the deviations from the normal range were of small extent and remained without clinical relevance. However, a slight trend towards reduction of the number of decreased values and corresponding rise of the number of increased values was noticed in total cholesterol and triglycerides at the end of treatment. There were very few abnormal values in 2 parameters which reached the defined alert ranges. One increased potassium value of 8.6 mmol/L in one Subject (Group A) was within the alert range (<3 or >6.1 mmol/L); the reason was specified by the laboratory as "pre-analytic problems" and thus not indicative of any pathological condition in this subject. Three increased leukocyte values (ranging from 14.3/nL to 16.4/nL) and 1 decreased value (2.4/nL) were within alert range (<2.8/nL or >14 /nL). Only the increased value of 14.3/nL in one Subject (Group A) was clearly associated with an AE (common cold); all other values within the alert ranges were of unclear etiology.

Conclusion(s)

As demonstrated in the present study, administration of the oral contraceptive Yaz in an extended flexible regimen (Yaz flexible regimen) produced considerable relief of dysmenorrheic complaints as compared to a conventional application scheme of the same medication and dosage. The therapeutic advantage of the extended flexible regimen was documented by significantly lower number of days with dysmenorrheic pain compared to the conventional regimen. Further confirmation of the superior efficacy of the extended flexible regimen was provided by markedly lower numbers of days with moderate to severe dysmenorrheic pain as well as days with pelvic pain (independent of occurrence of vaginal bleeding), days with dysmenorrheic pain associated with withdrawal bleeding, and days with interference of pain with daily activity. Taken together, this evidence suggests that long-term continuous OC treatment with the extended flexible regimen is capable to produce significant symptom relief in primary dysmenorrhea.

While several aspects of withdrawal bleeding (e.g., induction, duration, bleeding intensity) were comparable in both treatment regimens examined, the extended flexible regimen of OC treatment was associated with increased occurrence and average duration of intracyclic bleeding episodes. This observation is not unexpected, in view of existing knowledge that long-term progestin exposure of the endometrium is associated with cytological and vascular changes which may become manifest as transiently increased bleeding liability. The flexible regimen of Yaz allows the woman to react on breakthrough spotting and bleeding by inducing a withdrawal bleeding during the flexible phase (Days 25 to 120). With this strategy, she reduces the overall number of bleeding days and bleeding episodes as has been shown by the results of the present study.

Assessment of the global improvement of dysmenorrhea by the investigators and rating of the satisfaction with the study treatment by the subjects provided generally positive results for both regimens with a slight preference for the extended flexible regimen. Investigators' assessments of the degree of improvement of primary dysmenorrhea after treatment with the extended flexible regimen were slightly more favorable than the degree of treatment satisfaction expressed by the subjects.

The safety profile of BAY 86-5300 using an extended flexible regimen was comparable to the known OC safety profiles.

Publication(s):	None		
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Investigational Site List

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Sponsor in Germany	
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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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