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

Date of report:	29 APR 2013
Study title:	A multi-center, randomized, double-blind, active control, parallel-group, 2-arm study to investigate the effect of ethinylestradiol (EE)/ drospirenone (DRSP)(0.02 mg/3 mg) oral contraception (OC) in a 24/4 regimen compared to ethinylestradiol / desogestrel (DSG)(0.02 mg/0.15 mg) oral contraception in a 21/7 regimen on hormone withdrawal associated symptoms in otherwise healthy women after 4 cycles of treatment
Sponsor's study number:	14567
NCT number:	National Clinical Trial (NCT) number NCT01076582
EudraCT number:	2009-014911-11
Sponsor:	Bayer HealthCare AG
Clinical phase:	IIIb
Study objectives:	To show superiority of 24/4 OC (EE 0.02 mg / DRSP 3 mg) over 21/7 OC (EE 0.02 mg / DSG 0.15 mg) on hormone withdrawal associated symptoms after 4 cycles of treatment
Test drug:	BAY86-5300 / YAZ
Name of active ingredient(s):	ethinylestradiol, drospirenone
Dose:	0.02 mg ethinylestradiol / 3 mg drospirenone
Route of administration:	oral
Duration of treatment:	4 cycles of 28 days
Reference drug:	Mercilon
Dose:	0.02 mg ethinylestradiol / 0.15 mg desogestrel
Route of administration:	oral
Duration of treatment:	4 cycles of 28 days
Indication:	Oral contraception (hormone withdrawal associated symptoms)

Diagnosis and main criteria for inclusion:	Otherwise healthy women requesting oral contraception with a threshold for inclusion of a 50% increase of the composite score of hormone withdrawal associated symptoms headache, pelvic pain and bloating measured on a 7-point Likert scale during Days 22 to 28, versus the composite score during Days 1 to 21 (21-day score divided by 3 [for normalization])	
Study design:	Randomized, double-blind, active control, parallel-group, 2-arm study	
Methodology	Changes from Baseline to Cycle 4 in frequency and intensity of hormone withdrawal associated symptoms headache, pelvic pain and bloating measured on 7-point Likert scale	
Study center(s):	34 active centers in 14 countries : Argentina, Chile, Colombia, Czech Republic, Germany, Italy, Korea, Philippines, Portugal, Russia, Switzerland, Thailand, United Kingdom, and Venezuela	
Publication(s) based on the study (references):	None	
Study period:	First subject, first visit:	28 APR 2010
	Last subject, last visit:	28 OCT 2011
Early termination	Not applicable	
Number of subjects:	Planned:	550 women
	Analyzed:	592 full analysis set subjects (288 Yaz, 304 Mercilon) More details are given in the section on study subjects below.

Criteria for evaluation

Efficacy:

The primary efficacy variable was the change from Baseline to Cycle 4 in the sum of composite score during Cycle Days 22 to 28. The composite score comprised scores for headache, pelvic pain, and bloating (each measured by 7-point Likert scales).

The secondary efficacy variables were:

- change from Baseline to Cycle 2 in the sum of composite score during Cycle Days 22 to 28 (area under curve [AUC] of Days 22 to 28 for sum of 3 scores).
- change from Baseline to Cycle 4 and to Cycle 2 in the sum of individual scores during Cycle Days 22 to 28 (AUC of Days 22 to 28 for each score).
- change from Baseline to Cycle 4 and to Cycle 2 in number of days, where individual hormone-withdrawal symptoms are present on Cycle Days 22 to 28 (i.e. Likert Scale ≥1).
- change from Baseline to Cycle 4 and to Cycle 2 in maximum intensity of individual hormone-withdrawal symptoms on Cycle Days 22 to 28.
- individual scores and composite scores per cycle during Cycle Days 1 to 24 and during Cycle Days 25 to 28 for 24/4 OC.
- individual scores and composite scores per cycle during Cycles Days 1 to 21 and during Cycle Days 22 to 28 for 21/7 OC.
- rescue medication consumption.
- bleeding pattern.
- evaluation of questionnaires: Quality of Life Enjoyment and Satisfaction Questionnaire (short version), Clinical Global Impression.

Safety:

Safety variables in this study comprised:

- Adverse events and serious adverse events (SAEs)
- concomitant medication
- general physical and gynecological examination
- vital signs (heart rate and blood pressure)
- body weight, body mass index.

Other:	Other variables collected comprised compliance data from the diary cards, back-up contraception use from the diary cards, and use of pain medication.
Statistical methods:	The primary efficacy variable was analyzed as follows, all other variables were analyzed descriptively. It was assumed that the sum of composite scores during Cycle Days 22 to 28 was normally distributed. The change to Baseline was calculated as AUC4 - AUC0, where AUC4 denoted the sum of composite scores over Days 22 to 28 of Cycle 4 and AUC0 denoted the sum of composite scores over the Baseline Cycle (Cycle -1; Days 22 to 28). The null hypothesis H_0 (no positive treatment difference) was tested against the alternative hypothesis H_1 (treatment difference): H_0 : mean AUC4 - AUC0 (24/4 OC) = mean AUC4 - AUC0, (21/7 OC). H_1 : mean AUC4 - AUC0 (24 / 4 OC) ≠ mean AUC4 - AUC0 (21/7 OC). The null hypothesis was tested with a 2-sided type I error of 0.05.
Substantial protocol changes:	No protocol amendments became necessary.

Study subjects

A total of 714 subjects were screened for participation in this study. Of these, 120 subjects were screening failures. The most frequent reasons for screening failure was study criteria not met (57 subjects [47.5%]) and withdrawal of consent (34 subjects [28.3%]. The remaining 594 subjects were randomized as follows: 290 subjects Yaz and 304 subjects to Mercilon.

Full analysis set (FAS) consisted of 592 subjects (288 subjects in the Yaz treatment arm and 304 subjects in the Mercilon treatment arm). A total of 49 subjects (17.0%) in the Yaz treatment arm and 42 subjects (13.8%) in the Mercilon treatment arm experienced major protocol deviations and were excluded from the FAS, creating the per protocol (PP) population. This population included 239 subjects randomized to Yaz and 262 subjects randomized to Mercilon. Two subjects were randomized to the Yaz treatment arm but did not receive any study medication and were therefore excluded from the FAS and included only in the listing only set (LOS).

A similar number of subjects discontinued the study in both treatment arms (21 Yaz subjects [7.2%] and 19 Mercilon subjects [6.3%]). The most frequent reason for study discontinuation was “other” (9 Yaz subjects [3.1%] and 10 Mercilon subjects [3.3%]). Ninety-two percent (267 subjects) of Yaz subjects and 93.8% (285 subjects) of Mercilon subjects completed the study.

Subject demographic, gynecological and menstrual characteristics at baseline were balanced between the treatment arms. The mean (standard deviation =SD) age of subjects was 25.3 (4.4) years. Approximately one third (38.3%) of subjects were Caucasian, 28.9% were Hispanic and 32.8% were Asian. The mean (SD) body mass index (BMI) for the study population was 22.4 (2.95). Most subjects in the study never (44.6%) or only occasionally (36.0%) consumed alcohol and most (80.6%) were non-smokers. The majority (52.4%) had some college or university education and almost all (98.0%) were sexually active.

The most frequently reported medical and surgical history findings that were reported by >20% of subjects overall were abdominal distension (468 subjects [79.1%]), pelvic pain (522 subjects [88.2%]), headache (347 subjects [58.6%]), and drug-withdrawal headache (160 subjects [27.0%]). These findings are all in line with the target population ś inclusion criteria.

Efficacy / clinical pharmacology evaluation

Primary efficacy variable:

There was a decrease in composite score (comprising headache, bloating, and pelvic pain scores) from Baseline to Cycle 4. However, the treatment difference was not statistically significant and the superiority of Yaz compared to Mercilon could not be shown. Therefore the primary objective was not met.

For the primary endpoint, the difference between the treatment arms at Cycle 4 with regard to change in composite score from Baseline to Cycle 4 was not statistically significant (mean [SD] was -30.3 [22.9] for Yaz and -27.7 [24.8] for Mercilon, p = 0.2045 for the FAS). In absolute values, the mean (SD) of composite score was 12.8 [13.4] for Yaz and 14.3 [13.2] for Mercilon. A similar result was observed for the PP set.

Secondary efficacy variable:

There was an improvement in all individual symptoms from Baseline to Cycle 4. There was no treatment difference for change from Baseline to Cycle 4.

The overall percentage of subjects with hormone-withdrawal symptoms decreased in both arms from Baseline to Cycle 2 and Cycle 4 and fewer Yaz subjects than Mercilon subjects experienced symptoms during most cycle days. The maximum number of subjects experiencing symptoms during Days 22 to 28 was similar in both treatment arms.

There was a similar decrease in the maximum intensity of hormone-withdrawal symptoms in both treatment arms from Baseline to Cycle 2 and from Baseline to Cycle 4.

During the on-treatment period (Cycle Days 1 to 24 for Yaz and Cycle Days 1 to 21 for Mercilon) and the tablet-free period (Cycle Days 25 to 28 for Yaz and Cycle Days 22 to 28 for Mercilon) the individual scores for headache, bloating, pelvic pain, and the composite score for bloating and pelvic pain decreased from Baseline to Cycle 2 and to Cycle 4 in both treatment arms, indicating that symptoms improved. Yaz composite scores were consistently lower than Mercilon scores during the tablet-free period of Cycles 2 and 4, indicating that Yaz subjects experienced fewer and less intense combined symptoms during this time. The results of the composite score analysis were reflected in each of the individual score results.

The pattern of rescue medication consumption was similar in both treatment arms throughout the study. These numbers decreased from Baseline to Cycle 1 in both treatment arms and remained low (<32%) throughout the study. Of those who took rescue medication, most took the medication for only 1 day during all cycles.

Both treatment arms were similar with regard to bleeding/spotting and for spotting only patterns during the reference period (90 days). Subjects in both treatment arms experienced less spotting only than bleeding/spotting.

Most subjects in both treatment arms experienced withdrawal bleeding during the first 3 cycles. The length of withdrawal bleeding episodes remained consistent from cycle to cycle and was comparable for the 2 treatment arms (Yaz: 4.7 to 4.8 days; Mercilon: 5.0 to 5.4 days).

Overall, the percentage of subjects who experienced intra-cyclic bleeding during the study was low and similar in both treatment arms. Of those who experienced intra-cyclic bleeding, the majority in both arms experienced only intra-cyclic spotting or light bleeding during the first 3 cycles.

According the results of the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q) and Clinical Global Impression (CGI) questionnaires, the quality of life of subjects on both treatment arms improved to a similar degree over the course of the study from Baseline to Cycle 4.

Post-hoc analysis of the average of the 3 highest values of headache, bloating, and pelvic pain (analyzed individually), revealed that there was a reduction in all 3 symptoms over the course of the study in both treatment arms. The treatment difference was statistically significant in favor of Yaz at Cycles 2 and 3 ($p = 0.0023$; $p = 0.0055$).

A total of 76.2% of Yaz subjects and 75.0% of Mercilon subjects were found to be responders to treatment (as defined by an improvement in the most severe symptom of at least half the SD and no increase in rescue medication use during Cycle Days 22 to 28 from Baseline to Cycle 4 in the FAS).

Safety evaluation

The percentage of subjects with pre-treatment adverse events (AEs) was balanced between the treatment arms (Yaz: 19.4%; Mercilon: 23.0%).

The incidence of treatment-emergent adverse events (TEAEs) was similar in both treatment groups (Yaz: 31.3%; Mercilon: 29.9%) and the majority of subjects reported mild or moderate TEAEs.

The frequency and types of TEAEs were very similar in both treatment arms. The overall percentage of subjects with TEAEs was balanced between the treatment arms. The most common TEAEs (headache, nasopharyngitis, pelvic pain, abdominal distension) occurred with similar frequencies in both treatment arms. Headache and pelvic pain in the Yaz treatment arm, and headache and abdominal distension in the Mercilon treatment arm were the most common drug-related TEAEs that occurred.

There were no deaths in the study.

There were 3 SAEs in the study. Two of the 3 SAEs occurred in the Mercilon treatment arm and were unrelated to study drug (pyelonephritis and tonsillitis). One of the subjects who experienced pyelonephritis discontinued the study due to this SAE. The third SAE that occurred in the Yaz treatment arm was a spontaneous abortion which was considered to be related to the study drug. This was the only pregnancy reported during the study.

Other evaluations

Treatment compliance was high in both treatment arms with 96.36% compliance in the Yaz arm and 98.06% in the Mercilon arm.

Overall, the percentage of subjects who used back-up contraception remained low and balanced between the treatment arms throughout the study. In total, 17 subjects (2.9%) used back-up contraception method at Baseline. The use of back-up contraception increased at Cycle 1 to 18 subjects (3.1%) overall, which decreased to 7 subjects (1.2%) overall, at Cycle 4.

A total of 250 subjects (86.8%) in the Yaz treatment arm and 262 subjects (86.2%) in the Mercilon treatment arm took at least 1 concomitant medication. There were no obvious differences between the treatment arms regarding the class and frequency of concomitant medications. The most frequent concomitant medications (Anatomical Therapeutic Chemical (ATC) classification subclass), that were taken by ≥25% of subjects overall, were sex hormones and modulators of the genital system (357 subjects [60.3%]), analgesics (187 subjects [31.6%]), and anti-inflammatory and antirheumatic products (177 subjects [29.9%]). As stated the protocol, symptom relieving medication (rescue medication) was allowed in this study during study drug treatment.

Overall conclusions

The 24/4 OC, Yaz is effective in reducing the hormone-withdrawal symptoms of headache, bloating, and pelvic pain from Baseline to Cycle 4, however the superiority as compared to the 21/7 OC, Mercilon cannot be statistically shown. This result was reflected in the post-hoc analyses of the Asia/Pacific region and the European region. In contrast, the superiority of Yaz could be shown for the Latin American region. The incidence and intensity of withdrawal bleeding for the study population was as expected and moderate in both treatment arms. The incidence of intra-cyclic bleeding was low and similar in both treatment arms. Both treatments were well tolerated by the study population. No new safety signals emerged as a result of this study.

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

Date of last Update/Change: 09 Apr 2013

Investigational Site List

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