Clinical Study Synopsis

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Bayer HealthCare

Clinical Trial Results Synopsis

Date of report:	16-SEP-2013
Study title:	A multicenter, open-label, randomized, controlled, two-arm study to assess compliance with daily tablet intake of women on treatment with the oral contraceptive SH T00186D/BAY 86-5300 (0.02 mg ethinyl estradiol as betadex clathrate and 3 mg drospirenone) in a flexible extended regimen supported by a dispenser (CADDY) with a reminder function over 12 months
Sponsor's study number:	14701
NCT number:	National Clinical Trial number NCT01257984
EudraCT number:	2010-019902-17
Sponsor:	Bayer HealthCare AG
Clinical phase:	3
Study objectives:	The objective of the study was to evaluate the effect of the dispenser's acoustic alarm (buzzer) function on compliance with daily tablet intake when administered for approximately 12 months to healthy female volunteers between 18 and 35 years of age (inclusive) who requested contraception; when smoking, subjects were to be not older than 30 years at the time point of informed consent. In addition, the efficacy and safety of the oral contraceptive SH T00186D/ BAY 86-5300 (0.02 mg ethinyl estradiol (EE) as betadex clathrate [β-CDC] and 3 mg DRSP) was evaluated in a flexible extended regimen administered using a compliance-aiding dispenser (CADDY).
Test drug: **Name of active ingredients:** **Dose:** **Route of administration:** **Duration of treatment:**	EE/DRSP (YAZ Flex, BAY 86-5300) Ethinyl estradiol (EE) as betadex clathrate (β-CDC) / Drospirenone (DRSP) 0.02 mg EE as betadex clathrate (ß-CDC) / 3 mg DRSP in a tablet form (1 tablet/day) for up to 120 days, followed by a 4-day tablet-free interval Oral 12 months
Reference drug:	Not applicable
Indication:	Contraception
Diagnosis and main criteria for inclusion:	Healthy female volunteers between 18 and 35 years of age (inclusive) (smokers not be older than 30 years at the time point of informed consent), who requested contraceptive protection.

Study design:	Multicenter, open-label, randomized, controlled, 2-arm study (dispenser's acoustic reminder function ***on*** versus ***off***).
Methodology:	A tablet dispenser with a reminder function (CADDY) was used to improve compliance with daily tablet intake and to facilitate compliance with the specific requirements of the flexible extended regimen of YAZ Flex (mandatory and flexible intake phases, 4-day break). The dispenser reminded the woman visually with symbols and – only in arm A - with an acoustic signal at the time when tablet intake was due. The CADDY registered the daily tablet release time. Arm B - Group with inactivated CADDY acoustic reminder function (deactivated buzzer)
Study centers:	42 recruiting centers in 5 European countries: France (10), Germany (9), Italy (11), Spain (5), United Kingdom (7).
Publication based on the study (references):	None
Study period:	**First subject, first visit:** 23 DEC 2010 **Last subject, last visit:** 25 SEP 2012
Early termination:	No
Number of subjects per treatment group:	Planned: 500 subjects, 250 per treatment arm Analyzed: 535 enrolled subjects; 508 randomized subjects; 499 subjects in the full analysis set (FAS), 250 subjects in treatment arm A (activated buzzer) and 249 subjects in treatment arm B (deactivated buzzer); 363 subjects in the per protocol set (PPS), 160 subjects in treatment arm A (activated buzzer) and 203 subjects in treatment arm B (deactivated buzzer).
Criteria for evaluation **Efficacy:**	Primary efficacy evaluation was based on the mean daily delay of tablet release compared to reference tablet release time over 12 months in both treatment arms. Secondary: number of delayed/missed tablets, bleeding pattern and cycle control, the length of the tablet break and the length of the bleeding episode preceding the tablet break (i.e. length of managed unscheduled bleeding episode), questionnaires on CADDY, satisfaction with menstrual cycle and treatment, compliance and number of unintended pregnancies
Safety:	AE monitoring, gynecological examination including cervical smear, vital signs and body weight.

Statistical methods:	Primary efficacy variable was the mean daily delay time of tablet-release over 12 months. The delay time was the difference between the time of tablet release and the reference tablet release time, if the tablet release was after the scheduled tablet release time. Otherwise it was zero, i.e. there was no delay in tablet release. In the primary statistical comparison, mean daily delay of tablet release in both treatment arms was compared using an ANOVA. All secondary variables were analyzed descriptively. In case confidence intervals (CI) were calculated, they were 2-sided 95% CIs. Descriptive statistics were used for safety analysis. MedDRA version 15.0 was used for coding the adverse events.

Study subjects

A total of 535 female subjects from 42 study centers in 5 countries signed informed consent and were enrolled. Among them, 27 subjects failed screening and 508 subjects were randomized to treatment arm A (with activated acoustic alarm function of the CADDY) or treatment arm B (deactivated buzzer). A total of 9 randomized subjects never administered study drug.

The remaining 499 subjects (250 subjects in treatment arm A, 249 subjects in treatment arm B) were assigned to the full analysis set (FAS). Study medication and study were completed by 416 subject (207 subjects treatment arm A, 209 subjects treatment arm B). A total of 83 subjects (16.5% of the FAS) prematurely discontinued the study treatment. The main reasons for discontinuation were *adverse events*[1] for 31 subjects (6.2%) and *withdrawal by subject* for 23 subjects (4.6%). The FAS that included all subjects who administered the study drug was used to analyze safety. It also was the main set to analyze efficacy.

The population without major protocol deviations made up the per protocol set (PPS), comprising a total of 363 subjects (160 subjects/64.0% treatment arm A, 203 subjects/81.5% treatment arm B). The difference between both treatment arms was mainly due to the fact that 59 subjects in treatment arm A, who had more than 20% of their tablet releases occurring with a deactivated acoustic alarm, were excluded from the PPS.

Demographic and baseline characteristics were well-matched in both treatment arms. The mean ($\pm$SD) age of the FAS was 25.5 $\pm$4.1 years, mean body mass index (BMI) was 22.52 $\pm$2.98 kg/m^2. As requested by the entry criteria, no subjects older than 35 years (30 years in case of smokers) or with a BMI $\geq$ 30 kg/m^2 were included. The largest proportion of subjects in the FAS were white (86.4%) and for 13% of the subjects the race was not reported or missing.

[1] Including 1 subject whose non-treatment emergent AE started before any study drug was administered

Efficacy evaluation

The primary efficacy analysis showed superiority of treatment arm A with its activated acoustic alarm function compared to treatment arm B with deactivated buzzer. The mean estimated treatment difference of -1:30 hours (95% confidence interval -1:53 to -1.06 hours, FAS) in favor of treatment arm A was of statistical significance (p-value < 0.0001, 1-factorial ANOVA). It resulted from a mean delay in tablet release of 1:28 hours in treatment arm A compared to 2:58 hours in treatment arm B.

Several sensitivity analyses were performed and showed robustness of the result. In the FAS, the mean estimated treatment differences ranged from -1:30 to -1:05 hours in favor of treatment arm A. In the PPS, with a range from -1:45 to -1:19 hours the mean estimated treatment differences were even more pronounced than in the FAS (all analyses confirmed superiority, indicated by p-value < 0.0001).

The evaluation of the number of delayed and missed tablets confirmed the result of the primary efficacy analyses. Mean numbers of delayed or missed tablets were lower in treatment arm A with the activated acoustic alarm function compared to treatment arm B.

Regardless of the treatment arm, the CADDY with its compliance-aiding features supported the proper use of YAZ Flex (0.02 mg EE / 3 mg DRSP) by all women. The proportion of instruction-conform cycles (91.6%) recorded in the patient diary indicated a good support of treatment compliance by the CADDY. Less than 1% of all treatment cycles had tablet breaks longer than 7 days. Those cycles are critical as contraceptive efficacy of YAZ Flex, similar to all other hormonal oral contraceptives of this type, can no longer be guaranteed.

The mean cycle length (49.9 days) was roughly 2 times longer than the standard regimen of 28 days (24 days tablet intake and 4 days tablet break). The median cycle length of 34 days indicated that a large number of subjects did not take advantage of the possibility to increase the cycle length. By-country analysis showed that periods of tablet intake were longest in Germany (mean 69.91 days) and shortest in Spain (30.43 days), indicating that the Spanish women rarely deviated from the standard length of tablet intake of 24 days.

Normalized to one year of treatment, the mean number of bleeding/spotting days was 50.4 days. As expected due to the differences in cycle length between countries, also the bleeding pattern showed by-country differences. Those women who choose to extend their menstrual cycle will reduce the total number of days of bleeding over time. Women in Germany who extended their cycles the most had the lowest number of bleeding/spotting days (mean 40 days, median 36 days). In contrast, women in Spain who had more, but shorter cycles within the 1-year treatment period, reported the highest number of bleeding/spotting days (mean 68 days, median 61.5 days).

For subjects with scheduled bleeding, the mean length of the episodes was fairly stable (4.7 to 4.9 days for cycle 2 to cycle 10). The mean length of managed unscheduled bleeding episodes was longer (13.1 days at cycle 1 to 9.1 days at cycles 8 and 10). The percentage of subjects with unscheduled bleeding episodes (including spotting) was greatest at cycle 1 and lower for the remaining cycles (30.9% at cycle 1 to 7.4% at cycle 10).

Results of the questionnaire showed that the women considered the use and functionalities of the CADDY to be easy and clear. The majority of all ratings were positive. Some women suggested improvements of the CADDY, e.g. recommended a smaller size.

The menstrual bleeding survey was performed at baseline and again after 23 and 51 weeks of treatment. Results indicated improvements for most of the subjects. For example, the subjects satisfaction with the severity of their menstrual cycles increased (69.6%, 80.6%, and 79.5% agreed or strongly agreed at baseline, week 23, and week 51, respectively). The percentage of subjects increased who disagreed that the timing of the current menstrual cycle interfered with planned events (55.1%, 75.9%, and 83.0% disagreed or strongly disagreed at baseline, week 23, and week 51, respectively).

Also the treatment satisfaction survey confirmed the overall satisfaction with YAZ Flex. For example, most subjects agreed or strongly agreed that the cycles were of a suitable length, that they liked the low hormone dose and fewer menstrual bleedings, and less problems with menstrual bleeding. They disagreed or strongly disagreed that the intake regimen was too complicated or that irregular bleeding would harm their body. Consequently, the majority of all subjects would use this birth control once it is available on the market or would recommend it to a friend.

With no pregnancy[2] reported during 424 women years of relevant exposure, the Pearl Index was 0.00 (95% confidence interval 0.00 to 0.87) and confirmed that YAZ Flex is a reliable contraceptive.

Safety evaluation

The planned 1-year treatment duration was in the mean 336.6 days (median 367 days). Most women (60.5%) had a treatment duration of ≥ 364 days, followed by 25.3% who had a treatment duration of 290 to 363 days.

During this period 61.5% of the women experienced at least one treatment-emergent adverse event (TEAE). Most had TEAEs assessed by the investigator as not related to study drug and mild or moderate in intensity. The most common TEAEs, by descending order of frequency, were headache, nasopharyngitis, vomiting, breast pain, cystitis, and influenza. These types of AE were expected in this population of young and healthy women receiving an oral contraceptive.

The most common TEAE causing discontinuation was (study-drug related) *headache* in 1.2% of the subjects. All other TEAEs occurred in less than 1% of all subjects. A total of 12 subjects (2.4%) reported treatment-emergent serious adverse events (SAEs). Two subjects discontinued the study due to SAEs (one because of *ileal stenosis*, another because of *deep vein thrombosis* and *pulmonary embolism*). No death occurred.

To be included in this trial, subjects had to present with normal cervical smear results. During or after study treatment, 19 subjects had *cervical dysplasia* or *cervix smear abnormal* that were all considered unrelated to the study drug. Other TEAEs of special safety interest were

[2] Any pregnancy with a conception date on or after the first tablet intake until 4 days after the last tablet intake was considered. Actually, the first post-treatment pregnancy occurred 12 days after last tablet intake.

sudden hearing loss, lymphadenopathy, syncope, ulcerative colitis, cranial neuritis, and rectal hemorrhage in 1 subject, each; all were considered as not related to the study drug YAZ Flex.

Mean values of the vital signs (blood pressure and heart rate) showed no clinically relevant changes during the study. For 1 subject mild, unrelated tachycardia was reported as TEAE that caused the premature study termination. The mean body weight differed by 0.5 kg or less between the visits. *Increased weight* was reported as TEAE for 10 subjects. In 8 subjects it was regarded as study-drug related and in 3 subjects the (related) event caused a premature study termination. *Decreased weight* was reported for 2 subjects; in 1 subject it was regarded as study-drug related and caused the premature study termination. Unrelated *overweight* was reported for 1 subject and did not cause a premature study termination.

Overall conclusions

The acoustic reminder function of the CADDY reduced the mean delay of daily tablet intake by about 50%, i.e. one and a half hours. Without buzzer, there were almost 3 times as many missed tablets as with the buzzer. Overall women showed a good compliance with daily tablet intake and the treatment regimen.

No pregnancies under treatment occurred during a one year treatment of approximately 500 women (424 women years: Pearl Index 0.00, confidence interval 0.00-0.87). Those women who used the option of this flexible regimen of YAZ Flex to extend their cycle lengths experienced the benefit of a reduced total number of bleeding days compared to a standard regimen of YAZ.

The YAZ Flex regimen showed a safety profile consistent with combined oral contraceptives containing a low estrogen dosage of 0.02 mg ethinyl estradiol combined with 3 mg of the progestogen drospirenone. Over one year of treatment it was safe and well tolerated in the population of young and healthy women.