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.

Date of study report:	14 MAY 2007
Study title:	Multi-center, open, randomized, parallel group comparison of cycle control for seven cycles and endometrial safety in a subgroup for thirteen cycles of contraceptive patch SH P00331F (0.9 mg ethinylestradiol/1.9 mg gestodene) vs. a contraceptive comparator patch (0.6 mg ethinylestradiol/6 mg norelgestromin) in 400 healthy female volunteers
Sponsor's study number:	91402 (307969)
NCT number:	NCT00185354
EudraCT number:	2004-000821-31
Sponsor:	Bayer HealthCare
Clinical phase:	Phase III
Study objectives:	The objective of this study was to describe the bleeding pattern, cycle control, tolerability, and endometrial safety of the contraceptive patch SH P00331F vs. the comparator patch.
Test drug:	Ethinylestradiol and gestodene (SH P00331F, BAY 86-5016)
Name of active ingredient(s):	Ethinylestradiol (EE), gestodene (GSD)
Dose:	One patch of 10 cm^2 active area contained 0.9 mg EE + 1.9 mg GSD. A total of 50 µg of GSD and 17 µg of EE was released in 24 h
Route of administration:	The transdermal patches were applied onto clean, dry, intact and preferably hairless skin of the lower abdomen (below the navel) or buttocks. The patch application was preferably started on the right side, then with each subsequent patch alternating between left and right sides.
Duration of treatment:	One transdermal patch per week for 3 weeks followed by a patch-free period of 7 days (defined as 7 × 24 h equal to 6 calendar days). Each subsequent cycle was to start immediately after the previously completed cycle without a break between the cycles. Each cycle was to last a total of 28 days. Seven cycles were to be completed by subjects except in the biopsy subgroup, where the SH P00331Fwas used for a total of 13 cycles.
Reference drug:	SH P 331 N/Comparator patch/Evra
Dose:	One patch of 20.25 cm^2 active area contained 0.6 mg EE/6 mg norelgestromin (NGM). A total of 150 µg of NGM + 20 µg of EE was released in 24 h
Route of administration:	The transdermal patch was applied onto clean, dry, intact, and preferably hairless skin of the lower abdomen (below the navel), buttocks, and upper outer arm. The patch application was preferably started on the right side, then with each subsequent patch alternating between left and right sides.
Duration of treatment:	One transdermal patch per week for 3 weeks followed by a patch-free period

	of 7 days (defined as 7 × 24 h equal to 6 calendar days). Each subsequent cycle was to start immediately after the previously completed cycle without a break between the cycles. Each cycle was to last a total of 28 days. Seven cycles were to be completed.
Indication:	Contraception
Diagnosis and main criteria for inclusion:	Healthy female subject requesting contraception, aged between 18 and 35 years (inclusive), smokers maximum age of 30 years at inclusion
Study design:	This was a multi-center, open, randomized, parallel-group comparative study. Blinded study design was not possible due to the totally different matrix and shape of the patches.
Methodology:	Subjects were randomized to receive either SH P00331F or the comparator patch as study medication. The first patch of the first treatment cycle was applied on the first day of withdrawal bleeding (=first day of Cycle 1) both for starters (hormonal contraception) and switchers from a combined oral contraceptive. Patch application and removal took place on the same weekday, on cycle Days 8 and 15 at about the same time of the day. On cycle Day 22, the last patch of the cycle was removed followed by a 7 day patch-free period (defined as 7 × 24 h which equals 6 calendar days in the bleeding diary). On the first day of the following cycle, the next patch was applied and the procedure repeated, resulting in 3 patch-wearing periods and 1 patch-free period per cycle. In order to monitor compliance, cycle control, and bleeding, the subjects were asked to record every patch application and removal, reason for patch removal, number of new patches applied per day and bleeding events. At each visit, the completed diary cards were collected, reviewed, and signed by the investigator. The data on bleeding pattern and cycle control (efficacy variables) were collected using diary cards. A human chorionic gonadotropin (HCG)-urine test for pregnancy detection was performed by the subject. If throughout the study the pregnancy test proved positive, the study medication was stopped immediately. At the final visit (Visit 5/Visit 7) an HCG-urine test was performed in order to detect pregnancies at end of the study All pregnancies occurring in the course of the study were followed up for the final outcome of both mother and child. General safety was assessed by the investigator during the visits by examining and interviewing the subject. The occurrence of adverse events (AEs) or change in concomitant medication was recorded. During the pretreatment phase, acute abnormal findings as well as ongoing diseases or symptoms were documented as “baseline findings.” A complete physical examination was performed during Visits 1 (Screening), 5 (after Cycle 7), and 8 (after Cycle 13 only for biopsy group). Blood pressure, heart rate, and body weight were to be measured during the physical examination at Visit 1 and at every regular visit thereafter. Gynecological examinations including breast examination by palpation were performed at Visits 1 (Screening), 5

	(after Cycle 7), and 8 (after Cycle 13 only for the biopsy group). Cervical smears were taken at Visit 1 (Screening), Visit 5, Visit 8 (only for biopsy group) or in case of discontinuation. Endometrial biopsies were performed at admission (Visit 2) and during Cycle 13 (Visit 7), between Days 12 and 19. In case a subject belonging to the biopsy subgroup discontinued the study between Cycles 6 and 13, a second biopsy was obtained at the final examination, if possible. At the final examination, either in case of premature discontinuation or after Cycle 7 (Cycle 13 in the biopsy group), the subjective assessment of satisfaction and tolerability while using SH P00331F/Comparator patch was noted.
Study center(s):	The study was conducted at 28 centers in 4 countries: Austria (6), Finland (4), France (12) and Spain (6).
Publication(s) based on the study (references):	None at the time of report creation
Study period:	**Study Start Date:** 22 NOV 2004 **Study Completion Date:** 20 APR 2006
Early termination:	Not applicable
Number of subjects:	**Planned:** 400 subjects **Analyzed:** 416 subjects
Criteria for evaluation	
***Efficacy*:**	• Bleeding pattern (using reference periods of 90 and 30 days) was evaluated on the basis of number of bleeding/spotting days, number of spotting-only days, number, mean length, maximal length, range of length for bleeding/spotting episodes and spotting-only episodes • Cycle control (presented by cycle) included assessment of withdrawal bleeding indices (based on withdrawal bleeding incl. spotting [yes/no]; length, maximal intensity, and onset of withdrawal bleeding episodes) and intracyclic bleeding (with and without spotting) indices (based on intracyclic bleeding [yes/no]; number, maximal length, and maximal intensity of intracyclic bleeding episodes, number of intracyclic bleeding days). Cycle control was also presented for the number of subjects with at least 1 intracyclic bleeding episode in Cycles 2-6 for all subjects, or in Cycles 2-13 in the biopsy group. • Number of pregnancies
***Safety*:**	AEs were coded using both the Hoechst Adverse Reaction Terminology System (HARTS) Version 2.3 and the Medical Dictionary for Drug Regulatory Activities (MedDRA). The AEs were classified on the basis of seriousness, intensity, pattern, study drug relationship, study drug action, outcome of the AE, and duration of event. Laboratory values (hematology, general serum chemistry, liver enzymes,

	lipids, and glycosylated hemoglobin A [HbA1C]) outside the reference ranges and alert ranges were presented. Other safety variables including physical examination, gynecological examination (breast examination by palpation), baseline findings, blood pressure and heart rate measurements, body weight, cervical smear, endometrial biopsy, and HCG-urine test were also evaluated for abnormal findings. In addition, extent of exposure (days and months) was presented.
***Other*:**	Subjective assessment: A questionnaire was provided to the subjects at the final examination or in case of pre-mature discontinuation, to provide rating for overall satisfaction with the study medication, opinion on the acceptability of transdermal contraception throughout the study compared to the time before the study, tolerability and, if given a choice, whether she would have wished to continue with the study medication.
Statistical methods:	Analysis sets: The full analysis set (FAS) included all randomized subjects with at least 1 patch application and at least 1 observation after baseline. The per protocol set (PPS) was a subgroup of the FAS excluding subjects with major protocol deviations that potentially affected the primary endpoint. Efficacy variables (bleeding pattern and cycle control variables) were analyzed using both FAS and PPS. Safety and demographic variables were summarized using the FAS. Demographic and baseline parameters analysis: Summary statistics were presented for demographic and baseline variables. Efficacy analysis: The bleeding pattern and cycle control variables were analyzed using descriptive statistics (number of non-missing observations, mean, median, standard deviation (SD), minimum, 1st quartile, 3rd quartile, maximum) by treatment and reference period. In addition, frequencies (number and percentage) by treatment and cycle were measured for cycle control parameters. The failure rate, i.e., the probability of getting pregnant, was calculated on the basis of all pregnancies that became known within the framework of the study, including the follow-up. Safety analysis: A summary table for the extent of exposure by treatment group was presented. AEs were summarized by the number of subjects reporting at least one AE and by the actual number of events. Descriptive statistics were used to evaluate other safety parameters. The classification of physical/gynecological examination (normal or abnormal) was tabulated by treatment group and by time point (screening and final examination). The cervical smear results (normal or abnormal) and pregnancy test results were tabulated by treatment group and time point. Laboratory values, vital signs (systolic and diastolic blood pressure and heart rate) and body weight were summarized by visit and by change from screening. Other evaluation (Subjective assessment): Descriptive statistics and frequency tables were based on observed cases, i.e., subjects who have answered the questions.

Substantial protocol changes:	Amendment 1 from 28 APR 2005 introduced the following changes – change in timing of 2nd endometrial biopsy sampling, i.e., second biopsy sample in the endometrial biopsy subgroup was to be taken between Days 12 and 19 of Cycle 13 while the subjects still had the patch attached instead of "after Cycle 13." Consequently, one extra visit was scheduled for these subjects. Final examination (Visit 8) was to be performed 10-24 days after the last patch removal or premature termination instead of "12-19 days" after the last patch application. The amendment was applicable in study centers in Austria and in Finland.

Subject disposition and baseline

A total of 453 subjects were screened, of which 422 subjects were randomized, 210 subjects into the SH P00331F group and 212 subjects into the comparator group. The FAS included 416 subjects, 207 subjects from the SH P00331F group (including 81 endometrial biopsy subgroup subjects) and 209 subjects from the comparator group. The PPS was comprised of subjects who did not have any major protocol deviations that potentially could have affected the efficacy outcome, including 120 subjects from the SH P00331F group and 129 subjects from the comparator group. A total of 157 subjects (74.8%) in the SH P00331F group and 164 subjects (77.4%) in the comparator group completed the study medication. In the SH P00331F group, 52 subjects (24.8%), including 25 biopsy subgroup subjects, prematurely discontinued the study medication. In the comparator group, 46 subjects (21.7%) prematurely discontinued the study medication. Reasons for premature discontinuation of the study medication were specified as AE (SH P00331F: 29 subjects [13.8%], comparator: 24 subjects [11.3%]), lost to follow-up (SH P00331F: 3 subjects [1.4%], comparator: 2 subjects [0.9%]), withdrawal of consent (SH P00331F: 2 subjects [1.0%], comparator: 4 subjects [1.9%]), protocol deviation (SH P00331F: 1 subject [0.5%], comparator: 3 subjects [1.4%]), and pregnancy (1 subject [0.5%] in the SH P00331F group). 'Other' reason was given by 16 subjects in the SH P00331F group and by 13 subjects in the comparator group. Among the 'other' reasons, patch-adhesion-related problems were reported by 6 subjects from the SH P00331F group and by 3 subjects from the comparator group. Study medication administration status was set to 'unknown' for 1 subject in the comparator group. In the SH P00331F group, most of the study medication discontinuations took place during Cycle 2 (12 subjects). In the biopsy subgroup, 16 out of the 25 premature study medication discontinuations took place during cycles 1 through 5. In the comparator group, the discontinuations were more evenly distributed throughout the treatment period.

Study medication was never administered to 2 subjects (1 subject each from both treatment groups) and the reasons were specified as 'other' (SH P00331F, subject cannot attend study visits) and protocol deviation (comparator). These subjects were assigned to the listing only set (LOS) and they were not included in the statistical analyses. Mean (±SD) overall age of the subjects and BMI in FAS were 25.6 years (±4.6) and 22.4 kg/m^2 (±3.0), respectively, for comparator group and 25.2 years (±4.6) and 22.4 kg/m^2 (±2.8), respectively, for SH P00331F group. There were no differences in these variables between the treatment groups. The majority of the subjects were Caucasians and the majority of them, over 94%, did not use back-up contraception during the study.

Efficacy evaluation

In the SH P00331F group, the mean number of patches used per cycle ranged between 3.4 patches (SD 0.8, Cycle 3) and 3.9 patches (SD 1.1, Cycle 1). In the comparator group, the mean was 3.3 patches per cycle (SD 0.7), except for Cycle 6, where it was reported to be 3.4 patches (SD 0.7). The number of patches used per cycle by the biopsy subgroup was similar to that reported for the entire SH P00331F group; patch use stayed at an average of 3.4 patches per cycle during cycles 8 through 13. There was 1 subject who had used the patches for 14 cycles in the biopsy group. The results for bleeding pattern and cycle control here are presented for the 7-cycle comparative study (FAS). There were no further changes during the additional reference periods 3 and 4 in the biopsy subgroup.

Bleeding pattern: The bleeding patterns 'bleeding/spotting' and 'spotting-only' were characterized by the number of days and number of episodes, and the episodes themselves were further characterized by mean, maximum, and range of length of the episodes during 90- and 30 day reference periods. Only the 90 day reference period results on the bleeding pattern are summarized here. The mean values studied were very similar in both treatment groups, but there were some instances where the treatments varied slightly. In the SH P00331F group, the mean length of bleeding/spotting episodes was slightly lower in reference period 2 compared to reference period 1 (4.9 days [SD 1.4] vs. 5.4 days [SD 2.0]), and also lower than that in the comparator group in reference period 2 (5.4 days [SD 1.2]). In addition, the mean for maximum length of bleeding/spotting episodes was shorter in both groups in the reference period 2 compared to reference period 1 (SH P00331F: period 1: 7.8 days [SD 5.0] vs. period 2: 6.0 days [SD 2.4]; comparator: period 1: 7.4 days [SD 3.7] vs. period 2: 6.4 days [SD 2.2]). The means for the number of spotting-only days and the number of spotting-only episodes were similar between the treatments and lower in the reference period 2 in both groups. There was no difference in the mean length of the spotting-only episodes between the treatments in either reference period (SH P00331F: period 1: 2.6 days [2.3], period 2: 2.2 days [1.3]; comparator: period 1: 2.5 days [1.5], period 2: 2.7 days [1.7]) but the mean for the maximum length in reference period 2 was lower in the SH P00331F group (2.2 days, SD 1.4) than in the comparator group (3.2 days, SD 1.9).

Cycle control: In both treatment groups, a clear majority of the subjects experienced withdrawal bleeding in cycles 1-6, and there were no important differences between the treatments. In both treatment groups, the mean length of withdrawal bleeding episodes was around 5 days, and the mean onset was about 3 days after the removal of the last patch. The maximum intensity for withdrawal bleeding was rated as 'normal' bleeding by the majority of the subjects (64%-76.5%) in both treatment groups across the cycles 1-6. The proportion of subjects with 'light' withdrawal bleeding was greater in the SH P00331F group than in the comparator group (11.6%-21.5% vs. 10.1%-15.3%). In both treatment groups, the proportion of subjects with 'heavy' withdrawal bleeding was the largest in Cycle 1 (SH P00331F: 22.3%, comparator: 20.1%) and decreased thereafter to 9.7%-13.1% in the SH P00331F group and to 11.1%-19.1% of the subjects in the comparator group for Cycles 2-6.

Intracyclic bleeding was most common in Cycle 1 in both treatment groups, and it decreased thereafter. The proportion of subjects with intracyclic bleeding was larger in the SH P00331F group (Cycle 1: 21.4%, cycles 2- 6: 7.3%-10.8% of the subjects) than in the comparator group (Cycle 1: 15.8%, cycles 2- 6: 5.9%-12.1%). The mean number of intracyclic bleeding episodes was similar in both treatment groups (1.0-1.3 episodes), but there were fewer intracyclic bleeding days in the SH P00331F group in Cycles 1-6 (2.4 days [SD 2.1] to 5.8 days [SD 5.7] vs. 3.7 days [SD 4.2] to 6.1 days [SD 4.6]). In both groups, the maximum length varied from cycle to cycle without a clear trend. The mean for maximum

length of intracyclic bleeding episodes was shorter in the SH P00331F group compared to the comparator group in cycles 1-6 (SH P00331F: 2.4 days [SD 2.0]-5.8 days [SD 5.9] vs. comparator: 3.7 days [SD 4.2]-6.3 days [SD 5.8]). The majority of the subjects in both groups (42.9%-94.4%) assessed the maximum intensity of their intracyclic bleeding as 'spotting' in cycles 1-6. 'Normal' bleeding was the second most common intensity rating. There was less 'light' intracyclic bleeding in the comparator group (0%-16.7%) than in the SH P00331F group (6.3%-25.0%). 'Heavy' intracyclic bleeding was experienced only by very few subjects in both groups.

Number of pregnancies: There were 2 pregnancies in the SH P00331F group during the treatment and none in the comparator group. One of the pregnancies was considered a user failure, while the other was classified as a method failure.

Safety evaluation

Adverse events: A total of 267 subjects (64.6%) reported altogether 623 AEs during the study, among them 138 subjects (67.6%) in the SH P00331F group reporting 311 AEs and 129 subjects (61.7%) in the comparator group reporting 312 AEs. The most common AEs occurring in more than 5% of subjects within a treatment group were for the SH P00331F group headache (12.6%), upper respiratory infection (12.1%), application site reaction (12.1%), breast pain (7.2%), and dysmenorrhea (5.3%). For the comparator group, breast pain (14.4%), headache (12.0%), application site reaction (11.5%), and upper respiratory infection (11.0%) were the most common AEs. Of these, breast pain occurred at a higher frequency in the comparator group (14.4%) than in the SH P00331F group (7.4%), while the other 4 most common AEs occurred at similar frequencies. The incidence of AEs was similar in the biopsy subgroup and the overall SH P00331F group.

The most frequent treatment-related AEs in all subjects combined (overall) were application site reactions (11.3%), breast pain (10.8%), and headache (3.1%). Drug-related application site reactions occurred at similar frequencies in both treatment groups: 11.8% for the SH P00331F vs. 11.0% for the comparator. The proportion of subjects with drug-related breast pain was 2-fold higher in the comparator group (14.4%) compared to the SH P00331F group (7.4%). Drug-related headaches, on the other hand, were slightly more frequent in the SH P00331F group (3.9%) than in the comparator group (2.4%). For most of the AEs in both treatment groups, the main pattern was continuous, and the intensity was assessed as mild or moderate by the investigators. Specific drug treatment because of AEs was given to 45.6% of subjects in the SH P00331F group and to 35.4% of the subjects in the comparator group. Most subjects recovered from their AEs: 59.9% in the SH P00331F group and 51.7% in the comparator group.

In the 7-cycle comparative study, a total of 54 subjects (13.0%) experienced AEs that led to discontinuation of the study medication, among them 29 subjects (14.0%) from the SH P00331F group and 25 subjects (12.0%) from the comparator group. The most common AE leading to discontinuation of study medication was application-site reaction. Discontinuation due to application-site reaction was more common in the SH P00331F group than in the comparator group: 13 subjects (6.3%) vs. 8 subjects (3.8%). In 13-cycle biopsy subgroup, the 3 most common study drug-related AEs were the same as in the comparative part of the study: application-site reaction, headache, and breast pain. In the biopsy subgroup, 14 subjects (17.3%) discontinued the study medication due to AEs, and application-site reaction was the reason for study medication discontinuation for 5 of these subjects (6.2%).

Serious AEs (SAEs) occurred in a small proportion of subjects. In the SH P00331F group, 7 subjects (3.4%) experienced 7 non-fatal SAEs. Of these, 3 SAEs were in the biopsy subgroup and only 1 of them took place after the 7-cycle comparative part of the study. In the comparator group, 3 subjects (1.4%) experienced 5 non-fatal SAEs. Most SAEs were not or unlikely related to the study medication according to both the investigator and sponsor. Overall, all the subjects also recovered from their SAEs, except one subject with an abnormal cervical smear. All subjects, except one with melanoma, continued their study medication irrespective of the SAE.

Clinical laboratory tests: Clinically relevant abnormalities/changes in laboratory values at screening were reported for 7 subjects in the SH P00331F group and for 6 subjects in the comparator group. At the final examination, clinically relevant abnormalities/changes in laboratory values were reported for 4 subjects (high leukocytes in 1 subject, high triglycerides in 2 subjects, and high triglycerides and cholesterol in 1 subject) in the SH P00331F group and for 5 subjects (abnormal triglycerides in 3 subjects, high cholesterol in 1 subject, and high gamma-glutamyl transferase in 1 subject) in the comparator group. In the biopsy subgroup, only 1 subject had a clinically relevant abnormality (abnormal leucocyte count) at screening, and there were no other clinically relevant abnormalities/changes at any other time point in this subgroup.

Other safety variables: General physical examination, breast examination, and gynecological examination findings were normal for the majority of subjects in both treatment groups at the time points studied. At screening, abnormal physical examination findings were reported for 3 subjects from the SH P00331F group including 2 biopsy subgroup subjects and for 4 subjects from the comparator group. At the final examination, abnormal physical examination findings were reported for 3 subjects in the SH P00331F group, including 2 biopsy subgroup subjects, and for 4 subjects in the comparator group. All of these changes were assessed as clinically significant changes from baseline. At screening, 1 abnormal breast examination was reported in the comparator group and specified as ‘lump in the left breast; size same as in the biopsy a year ago.’ At the final examination, an abnormal breast examination finding, which was also considered as a clinically significant change, was reported for another subject from the comparator group.

At screening, abnormal gynecological findings were reported for 1 subject from the SH P00331F group and for 5 subjects from the comparator group. At Cycle 7, abnormal gynecological findings were reported for 4 biopsy subgroup subjects. At the final examination, abnormal gynecological findings were reported for 4 subjects from the SH P00331F group including 2 biopsy subgroup subjects and for 1 subject from the comparator group. All the subjects had a normal cervical smear result at screening. At Cycle 7, 1 biopsy subgroup subject had an abnormal cervical smear result specified as Pap III 0. At the final examination, 2 subjects had abnormal cervical smear findings, which were specified as ‘some dysplastic cells’ (SH P00331F group) and ‘inflammation with unclear nuclear changes’ (comparator group).

At screening, endometrial biopsies were taken from a subgroup of 90 subjects in the SH P00331F group; they were assessed ‘normal’ for 81 subjects, ‘not assessable’ for 6 subjects, and ‘not available’ for 2 subjects. One subject was lost to follow-up after the screening. At Baseline, the 3 most common histological characteristics were ‘weakly proliferative’ (28.4% of the subjects), ‘disordered proliferative’ (25.9% of subjects), and ‘secretory, cyclic type’ (18.5% of subjects). At the final examination, the distribution of the histological characteristics was very different due to the time of the biopsy sampling (cycle days 12-19, inclusive). Almost half of the subjects (42.0%) had ‘inactive

endometrium,' and 13.6% had 'atrophic endometrium.' The endometrial biopsy was missing for 14 subjects (17.3%), 'not available' for 4 subjects (4.9%) and 'not assessable' for 2 subjects (2.5%) at the final examination. At baseline, 3 subjects had endometrial polyps, 1 subject had limited endometrial metaplasia, and 10 subjects had fragments of cervical tissue in the endometrial biopsy. At final examination, 1 subject had endometrial polyps, and 3 subjects had fragments of cervical tissue in their biopsies. Endometrial stromal tissue or inflammatory conditions were not present in any of the biopsies.

No changes in the mean body weight were observed during the study in either treatment group. In both treatment groups, the mean heart rate increased slightly from screening to Cycle 4 (or to Cycle 7 in the biopsy subgroup). The mean absolute change from baseline ranged between −0.6 beats per minute (bpm) (SD 12.6) and 0.6 bpm (SD 10.3) in the SH P00331F group and between −0.8 bpm (SD 13.3) and 0.1 bpm (SD 14.0) in comparator group. In the biopsy subgroup, mean absolute change from baseline ranged between −1.1 bpm (SD 11.4) and 0.8 bpm (SD 10.4).

The mean systolic blood pressure was steady during the study in both treatment groups, ranging from 116.8 mmHg (SD 10.1) to 119.2 mmHg (SD 11.9) in the SH P00331F group, and from 116.9 mmHg (SD 11.0) to 117.9 mmHg (SD 10.9) in the comparator group. The mean absolute changes from baseline were small and ranged from 0.7 mmHg (SD 12.8) to 2.1 mmHg (SD 11.1) in the SH P00331F group and from −0.1 mmHg (SD 9.6) to 0.5 mmHg (SD 11.9) in the comparator group. The mean diastolic blood pressure changed only very slightly during the study in both treatment groups, ranging from 70.8 mmHg (SD 9.2) to 71.8 mmHg (SD 9.9) in the SH P00331F group, and from 70.2 mmHg (SD 9.1) to 72.5 mmHg (SD 9.9). The mean absolute changes in diastolic blood pressure from baseline were small in both treatment groups, and ranged between 0.0 mmHg (SD 7.4) and 0.9 mmHg (SD 9.1) in the SH P00331F group and between −0.3 mmHg (SD 8.1) and 1.6 mmHg (SD 8.4) in the comparator group. The mean systolic blood pressure by visit and the mean absolute change from baseline for the biopsy subgroup were comparable to the values for SH P00331F in the 7-cycle comparative study. For the majority of the subjects in both treatment groups and at any visit, the changes in the systolic/diastolic blood pressure were less than +5 mmHg.

An HCG-urine test had to be performed by the subject at home before the first patch application. At final examination, a pregnancy test was conducted at the study center to detect pregnancies at the end of the study. This was performed for a total of 278 subjects, among them 143 subjects from the SH P00331F group and 135 subjects from the comparator group. In both treatment groups, 1 subject had a positive test result at the final examination. In the comparator group, this was a planned pregnancy, and the subject had discontinued the study earlier due to a desire to get pregnant.

Extent of exposure: In the comparative 7 cycle study, the mean exposure time was 5.4 months (SD 1.6) in the SH P00331F group, and 5.6 months (SD 1.6) in the comparator group. The mean exposure time in the biopsy subgroup was 9.9 months (SD 3.7).

Other evaluations

Subjective assessment: The satisfaction with the study treatment was high in both treatment groups: 76.3% of the subjects in the SH P00331F group and 73.6% of the subjects in the comparator group were satisfied (satisfied/very satisfied) with their treatment. In the SH P00331F group, 47.3% of the subjects and 41.6% of the comparator group subjects would have continued with the study treatment if given the choice. The ratings given for the color and size of the patch were more favorable in the SH P00331F

group than in the comparator group. In the comparator group, more subjects would have changed the color and the size of the patch than in the SH P00331F group.

Overall conclusions

In this study, SH P00331F provided a good and well-acceptable bleeding profile while also offering reliable and consistent cycle control, both of which were comparable to those experienced by the subjects of the comparator patch. The subjects of the SH P00331F patch tended to have shorter and lighter withdrawal bleeding periods compared to the comparator patch subjects. Slightly more subjects in the SH P00331 group experienced intracyclic bleeding, but the intensity of the intracyclic bleeding was lighter. In addition, subjects in the SH P00331F group had fewer intracyclic bleeding days than the comparator patch subjects. More subjects in the SH P00331F group discontinued the study drug because of application site reactions. The study drug-related breast pain was twice as common in the comparator group, but drug-related headaches were slightly more common in the SH P00331F patch group. There were no abnormal findings in the endometrial safety samples. The general safety profile of SH P00331F gave no reasons for any concerns. The AE profile did not show any unexpected events.