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.

2. Synopsis

Date of report:	29 APR 2014
Date Last updated:	21 May 2014
Study title:	**Multi-center, open-label, randomized study to assess the safety and contraceptive efficacy of two doses (in vitro 12 µg/24 h and 16 µg/24 h) of the ultra low dose levonorgestrel contraceptive intrauterine systems (LCS) for a maximum of 3 years in women 18 to 35 years of age and an extension phase of the 16 µg/24 h dose group (LCS16 arm) up to 5 years**
Sponsor's study number:	91665 (310442)
NCT number:	NCT00528112
EudraCT number:	2007-000420-40
Sponsor:	Bayer HealthCare AG, D-51368 Leverkusen, Germany
Clinical phase:	3
Therapeutic Area	Women's Healthcare
Study objectives:	The objectives of this study were to assess the safety, efficacy and pharmacokinetics of two doses of LNG (initial in vitro release rates of 12µg and 16µg per day), delivered locally by a new intrauterine contraceptive system suitable for use by women 18 to 35 years of age for up to 3 years. The safety, efficacy and pharmacokinetics of the LCS16 treatment arm were to be studied for up to 5 years.
Test drug:	Levonorgestrel (Jaydess, Skyla, BAY 86-5028
Name of active ingredient(s):	Levonorgestrel (LNG)
Dose:	Initial in vitro release rate: 12µg/24 h and 16µg/24 h
Route of administration:	Intrauterine
Duration of treatment:	3 years (5 years for LCS16)
Reference drug:	None
Indication:	Contraception

Diagnosis and main criteria for inclusion:	Generally healthy, 18 - 35 year-old nulliparous or parous women in need of contraception. Women in the LCS16 treatment group could be included in the extension phase up to 5 years if they so wished and if the investigator agreed to continue the study.
Study design:	Multi-center, open-label, randomized, 2-arm, parallel–group study up to 3 years Single arm, open-label study from 3 years up to 5 years (extension) for the LCS16 treatment group
Methodology	Monitoring of the occurrence of pregnancies. The number of pregnancies was recorded and pregnancy rate as Pearl Index (PI) was calculated as the primary efficacy variable in this study; a secondary analysis was performed using the Kaplan-Meier method. Vaginal bleeding was treated as a secondary efficacy variable. Vaginal bleeding was evaluated from the bleeding data obtained from subject-kept diaries. A user-satisfaction questionnaire was added in Amendment 3. The safety data included adverse events (AEs), the occurrence of dysmenorrhea (to be recorded in the diary), the evaluation of ease of LCS insertion and removal by the investigator and the evaluation of pain during LCS insertion and removal by the study subjects. Other variables were IUS expulsion rate and the overall discontinuation rate.
Study center(s):	Countries and number of recruiting study centers: Argentina (5), Canada (13), Chile (3), Finland (15), France (8), Hungary (8), Mexico (4), Netherlands (9), Norway (5), Sweden (11), USA (57)
Publication(s) based on the study (references):	Nelson A, Apter D, Hauck B, Schmelter T, Rybowski S, Rosen K, Gemzell-Danielsson K. Two low-dose levonorgestrel intrauterine contraceptive systems: a randomized controlled trial. Obstet Gynecol. 2013 Dec;122(6):1205-13. doi: 10.1097/AOG.0000000000000019 ~~None~~
Study period:	First subject, first visit: 20 AUG 2007 Last subject, last visit: 07 JUN 2013
Early termination	No

Number of subjects:	Planned:	1410 in each group (LCS12 and LCS16); in the extension phase in the LCS16 treatment group all women willing to continue after 3 years up to 5 years
	Analyzed:	2884 in the full analysis set (FAS) (LCS12: 1432, LCS16: 1452). From the total of 1452 subjects treated with LCS16, 707 continued in the extension phase. More details are given in the section on study subjects below.
Criteria for evaluation		
Efficacy / clinical pharmacology:	Primary variable: Pearl Index (PI) (pregnancy rate) Secondary: bleeding patterns; number of participants with/without ovulation; average total cervical score; classification of endometrium; degree of overall user satisfaction with study treatment; number of participants with partial or total expulsion	
Safety:	Adverse events, vital signs, dysmenorrhea, LCS insertion ease and pain, LCS removal ease and pain, safety laboratory.	
Other:	Not applicable	

Statistical methods:	Efficacy (Primary): The Pearl index (PI) was calculated using the model specified below. In addition, the corresponding 2-sided 95% CI was calculated. Mathematical model for the calculation of the PI: By assuming that the number of pregnancies follows a Poisson-distribution, the point estimate and the 95 % CI for the PI can be calculated as follows: PI = x/E, lower 95% confidence limit of PI = 0.5 x χ^2(0.025, 2x) /E, upper 95% confidence limit of PI = 0.5 x χ^2(0.975, 2(x+1)) /E, where x = number of pregnancies, E = exposure in 100 woman-years (one woman-year is 365 days of treatment exposure), $\chi^2_{(alpha,df)}$ is the alpha quantile from χ^2-distribution with df degrees of freedom. Additionally, PIs were also to be presented by parity, age-group and body mass index (BMI). As the expected number of pregnancies was low, no additional or more granular subgroup analyses were planned. To assess pregnancies with regard to subgroup combinations, e.g. by age and parity, a listing of all pregnancies providing detailed information on subject number, age, parity, date of intrauterine system (IUS) insertion, date of IUS removal, (estimated) date of (partial/total) expulsion, estimated date of conception, ectopic pregnancy (n/y), estimated date of conception relative to IUS insertion, date of estimated date of conception relative to end of study medication, and comments was provided. Efficacy (Secondary): A Pearl Index was also calculated for ectopic pregnancies only.As a secondary analysis the cumulative failure rate, i.e. the probability of getting pregnant, was calculated using the Kaplan-Meier method. Vaginal bleeding was recorded every day by the subjects using diaries provided by the sponsor. For subjects with evaluable bleeding diary data, descriptive statistics were used for evaluation of bleeding patterns, and WHO bleeding indices. Safety: AE terms were summarized by Medical Dictionary for Regulatory Activities (MedDRA) system version 16.0

Substantial protocol changes:	The study protocol, dated 28 Jun 2007, was amended six times. Amendment 1, dated 04 Oct 2007, was a local amendment for Hungary only. No subjects had been recruited in Hungary before the amendment came into effect. The amendment made the following modification: an additional exclusion criterion was added in order to exclude nulliparous women from participating in the study in Hungary. Amendment 2, dated 27 Jan 2008, contained the following global modifications: the wording of exclusion criteria was revised and an inconsistency was corrected in the text. The pregnancy test at the end of the study was changed from a serum to a urine test, the documentation procedure for normal pregnancies was revised, additional, annual cervical smears were added and the timelines for serious adverse events (SAEs) and pregnancy reporting were changed to within 24 hours. Amendment 2 also contained a modification that affected only North America (the USA and Canada):the transvaginal ultrasound that was to be performed at screening was deleted for these countries. Amendment 3, dated 16 Jan 2009, was implemented when all subjects had already been recruited. It specified the following global modifications: information on the educational background of study subjects at baseline was to be collected from all randomized subjects remaining in the study at the time amendment 3 came into effect, 'compliant' subjects were clarified as those in whom the LCS was correctly located in the fundal position (in situ) or in whom it was displaced but still in the uterine cavity (displaced, intrauterine), a user satisfaction questionnaire was added to the end-of-study visit, the visit window of the premature termination examination was clarified, the recording of adverse events with regard to main pattern and study drug action was clarified. In addition, there were changes to the study administrative structure and the name of the central laboratory in charge of the pharmacokinetic (PK) analyses was added. There were also one modification that affected Chile only (regarding the change of central laboratory) and one modification that affected Finland only (determination of serum silver ion concentration measurements in a subset of women (subset 3) were added).

Substantial protocol changes (continued):	Amendment 4, dated 07 Oct 2009, was a local amendment for North America only, and was implemented when all subjects had already been recruited. It contained the following modifications: change to the study administrative structure and change of the central laboratory in the USA and Canada. Amendment 5, dated 30 Nov 2009, was implemented when all subjects had already been recruited. It specified the following global modifications: treatment in the LCS16 treatment arm was extended up to 5 years, change of the dose-group names, clarification of the content of the pregnancy information package, clarification of the content of the SAE information package. changes to the study administrative structure and name from 'Drug Safety Unit' to 'Pharmacovigilance'. One modification affected Finland only: Attachment 1 was modified to incorporate changes due to the extension of treatment in the LCS16 arm up to 5 years in the already assigned study subsets. Amendment 6, dated 13 May 2013, was implemented when all subjects had already been recruited. It specified the following global modification: in the LCS16 arm, the number of returned LCS16 devices that were to be analysed for residual LNG content from subjects that completed the 5-year treatment was changed from all returned LCS16 devices to 345 LCS devices.

Study subjects

The subjects treated with LCS were women between 18 and 35 years of age, in good general health, and in need of contraception. A total of 3661 subjects were screened for inclusion in the study, leading to a total of 1432 subjects who were randomized to the LCS12 arm and to1453 subjects who were randomized to LCS16 treatment arm. One subject was randomized to the LCS16 group but no insertion was attempted and so she was excluded from the full analysis set (FAS) which therefore included 1452 subjects. The FAS, that included all subjects with at least one insertion attempt, was used for all efficacy and safety analyses. A pharmacokinetics analysis set (PKS) was defined for the subjects in subset 3 with valid data for PK analysis. At least one protocol deviation in 39 subjects (2.7%) in the LCS12 group, and in 26 subjects (1.8%) treated with LCS16 was assessed as major but did not lead to exclusion from the analyses. During the 3-year study, a total of 1193 women (41.4%; LCS12: 613, LCS16: 583 subjects) discontinued study medication prematurely. Of the 870 subjects that completed the 3-year treatment in the LCS16 treatment group, 707 subjects continued in the LCS16 extension phase. From these, 550 subjects completed study at year 5 (EOS), and 157 subjects discontinued study medication during the LCS16 extension (after Year 3).

Overall (including both treatment groups), 80.0% of women in the FAS were Caucasian. The mean age of the subjects was approximately 27 years (27.1 [SD 4.9]; range 18 – 35 years).

Almost 40% of the subjects were 25 years of age or younger and 39.5% of women were nulliparous (SD: standard deviation).

Efficacy / clinical pharmacology evaluation

In total, 2871 women had successful insertions (LCS12: 1426 women, LCS16: 1445 women). Of these, 2770 were successful at the first attempt and 101 were successful at the second attempt. Overall compliance, defined as a location of the intrauterine system (IUS) of either in situ or displaced, intrauterine (not in the fundal position but still completely within the uterine cavity), was high, and no differences in correct position of the IUS were seen between parous and nulliparous women at treatment visits, but there were more non-compliant at the end-of –study visits, as there were more expulsions in parous women. Non-compliance in this study indicated at least a partial expulsion of the LCS, examined in detail under "other evaluations".

A total of 10 pregnancies were observed on treatment during the **first 3 years in the LCS12 group** (see below for the pregnancies in the LCS16 group). Of these, 3 were ectopic. Of the remaining 7 pregnancies in the LCS12 group, 3 pregnancies ended in spontaneous abortion and 1 in induced abortion, 2 pregnancies were normal and carried to term and 1 pregnancy was delivered prematurely by cesarean section due to preeclampsia, with a normal fetal outcome. The earliest estimated date of conception was 40 days after insertion (one subject, LCS12) and the latest estimated date of conception was 1076 days after insertion (one subject, LCS16). During the first year of treatment with LCS12, 5 pregnancies occurred, during the second year, 3, and during the third year of treatment 2 pregnancies occurred.

The **relevant 3-year exposure** for the Pearl Indices (PI) was similar in the two treatment groups: 3058.62 woman years (WY) in the LCS12 group and 3211.36 WY in the LCS16 group. The unadjusted and adjusted 3-year PIs were identical (LCS12: 0.33, LCS16: 0.31). The upper limits of the 2-sided 95% CI were below 0.6 for both treatment groups. The unadjusted and adjusted Year-1 PI was equally favorable (LCS12: 0.41, LCS16: 0.16). The upper limits of the 2-sided 95% CI were below 1 for both treatment groups. The PIs by parity, age-group and BMI showed results similar to those for the overall population.

The cumulative failure rate over 3 years was 0.9% in the LCS12 group and 1.0% in the LCS16 group. The cumulative failure rates over 3 years by parity, age-group and BMI were equally favorable.

A total of 13 pregnancies were observed on **LCS16 treatment during the 5-year** treatment [2]. Of these, 8 pregnancies were ectopic. Of the remaining 5 pregnancies, 2 ended in spontaneous abortion, 1 ended in missed abortion and 2 pregnancies were normal and carried to term. The earliest estimated date of conception was 283 days after insertion (Subject 160423) and the latest estimated date of conception was 1076 days after insertion (Subject 243932). 2 pregnancies occurred during the first year, 4 during the second year, 4 during the third year, 1 during the fourth year and 2 during the fifth year of LCS16 treatment.
The **relevant exposure in the 5-year study** for the Pearl Indices (PI) was 4434.53 woman years. The overall PI, the primary efficacy endpoint, was favorable at **0.29** (95% CI [0.16; 0.50]). The PIs for the individual treatment years were similarly favorable, ranging from 0.16

[2] An additional pregnancy occurred during the study but after EOSM.

(year 1) to 0.45 (year 3). There were no relevant differences between the results of adjusted and unadjusted analysis. The PIs by parity, age-group and body mass index (BMI) showed results similar to those for the overall population. Due to small number of pregnancies is it difficult to draw conclusions from any small numerical differences.

The **cumulative failure rate over 5 years** in the LCS16 group was **1.4%** (95% CI [0.823; 2.531]) and in line with the cumulative failure rate over 3 years (1.0%) reported for subjects on LCS16. There were no relevant differences between the results of adjusted and unadjusted analysis. The cumulative failure rates over 5 years by parity, age-group and BMI were equally favorable.

During the **first 3 years** of treatment, in both treatment groups, **bleeding patterns**, analyzed by 90-day and 30-day reference periods, in days and in episodes, and for each 90-day reference period also by the WHO clinically important bleeding categories, showed a clear trend for an increase in the number of women with amenorrhea and infrequent bleeding over the course of the study. The number of women with frequent and prolonged bleeding decreased.

During the **5-year treatment** period in the LCS16 group, there was a decrease in the mean number of days in all categories of bleeding (bleeding/spotting, bleeding only and spotting only) and in the mean length of bleeding/spotting episodes. The analysis of bleeding by WHO categories was equally favorable, and the results were similar to those over 3 years of treatment. The proportion of subjects with amenorrhea and infrequent bleeding increased over the course of the 5 years. The incidence of prolonged bleeding and frequent bleeding decreased. The proportion of subjects with irregular bleeding also decreased during the 5-year treatment.

In both treatment groups, almost all subjects in whom ovulation was evaluated showed evidence of ovulation during the period studied in each treatment year (LCS12: Years 1 to 3, LCS16: Years 1 to 4; (no subjects remained in this subset at Year 5). Both treatments showed very similar progestogenic effects on the cervical mucus with low and comparable cervical scores over the 3-year treatment period. One subject (LCS16) remained in the subset 1 in Year 4 with a mean cervical score of 0.170. As expected, In both treatment groups, the progesterone effect on the endometrium was marked at all time points examined (LCS12: Years 1 ot 3, LCS16: Years 1 to 4; no subjects available at Year 5), indicating a high degree of endometrial suppression.

At baseline, histological classification of the endometrium was possible for 30/31 subjects in the LCS12 group, and for 28/29 subjects in the LCS16 group. In majority of them (LCS12: 28/30, LCS16: 26/29) the endometrium was proliferative and in 2 subjects in both treatment groups it was secretory. At Month 12, and At Month 24, endometrium was secretory in all subjects whose sample could be classified, at Month 36 (EOS), with the exception of one subject, all biopsies revealed a secretory endometrium and at month 48/EOS all biopsies demonstrated secretory endometrium.

The IUS expulsion rates were very low during the first 3-years in both treatment groups, which had similar numbers of partial and total expulsions (LCS12: 53 [3.7%], LCS16: 46 [3.2%]). Expulsions occurred at various times during the study treatment period, with a clear

trend for more expulsions during the first 12 months after insertion. Analyzed with the Kaplan-Meier estimator, the estimated cumulative probability of at least partial expulsion by Month 36 was 4.56% for the LCS12 group and 3.58% for the LCS16 group. More expulsions occurred in parous than in nulliparous women, and more occurred in women age ≤ 25 than in women age > 25 < 35.

The IUS expulsion rates were very low; total or partial expulsions were documented for 54 subjects (3.7%) treated with LCS16 up to 5 years (including the 46 expulsions noted above and an additional 8 expulsions reported during years 4 and 5). Over half of the expulsions (33/54) had occurred by Month 12 and majority (45/54) by Month 36. By Month 60, the estimated cumulative probability of at least partial expulsion was 5.02% (end of study) and the estimated cumulative probability of total expulsion was 1.80%.

Overall, of the 2116 of 2884 women (Month 36 - LCS12: N=1053; LCS16: N=1063) who were given a user satisfaction questionnaire (introduced after protocol amendment 3), a large majority (77.4%) were ‘very satisfied’ with study treatment (17.9% were ‘somewhat satisfied’), and 79.5% said that they were likely to continue treatment with LCS after the study. Ratings regarding the changes in menstrual bleeding, the menstrual bleeding pattern and menstrual pain were positive. The results were similar in the two treatment groups after 3 years of treatment. Most subjects (88.9%) in the LCS16 group were “very satisfied” with the treatment also after 5 years. A large majority of subjects would have continued with the LCS16 if given the choice after 3 years (82.1%) and after 5 years (85.1%) of treatment.

Safety evaluation

Neither LCS12 nor LCS16 was associated with any new or unexpected safety events, and both were generally well tolerated.

3-year results (LCS12 and LCS16)

A total of 2440 (84.6%) women reported at least 1 AE during the first 3-years, but there was a clear trend for fewer subjects reporting AEs over time (total almost 73% in the first year of treatment and a little over 50% in the second and third years). No clinically relevant differences were noted between treatment groups in the incidence of treatment-emergent AEs. The overall incidence of events of interest was low in both treatment groups

The most frequently reported AEs were: ovarian cyst (17.0%, due to the protocol requirement for ultrasound findings of cysts to be reported as AEs even if standard AE criteria were not met), acne (11.5%), and urinary tract infection (10.5%). The AEs most frequently classified as severe were pelvic pain (2.0%), abdominal pain (1.6%), dysmenorrhea (1.5%) and headache (1.4%). The AEs that most frequently led to withdrawal of study medication were vaginal hemorrhage (3.3%), device expulsion (2.8%), pelvic pain (2.4%), acne (2.2%), abdominal pain and dysmenorrhea (1.1% each). The treatment groups were affected similarly, with acne more frequent in the LCS12 group and pelvic pain slightly more frequent in the LCS16 group.

Study-drug-related AEs were reported in 50.8% of women. The only study-drug-related AE that occurred considerably more often in either of the treatment groups was ovarian cyst, which was reported for 201 women (13.8%) in the LCS16 group, and 110 women (7.7%) in the LCS12 group. This difference is plausible, as the lower systemic exposure to LNG in the

LCS12 treatment group may have less influence on the hypothalamic-pituitary axis than in the LCS16 group.

Serious adverse events (SAEs) in 23 women (0.8%) were reported by the investigator to be related to study drug. The most frequent study drug-related SAEs were ectopic pregnancy (9 women; 8 cases were considered study drug-related, plus one ruptured ectopic pregnancy also assessed as related to study drug) and pelvic inflammatory disease (PID) (6 women, all assessed as related to study drug treatment).

PID was diagnosed in 12 women in total, i.e. 6 SAEs and 6 non-serious AEs. Additionally, 6 women had a final diagnosis of pelvic infections that didn't meet the criteria defined in the protocol for PID and the other 7 had non-associated diagnoses.

5-year results (LCS16)

From a total of 1452 subjects treated with LCS16, 1286 subjects (88.6%) reported at least 1 adverse event (AE) during the 5-year study. More subjects (73.7%) reported AEs during the first year of treatment than in the Year 2, 3 ,4 or 5 (all ≤55.5%).

Most common AEs reported in subjects treated with LCS16 were: ovarian cyst (23.3% due to the protocol requirement for ultrasound findings of cysts to be reported as AEs even if standard AE criteria were not met) , acne (12.3%), urinary tract infection (11.5%), vaginitis bacterial (10.3%), headache (10.1%) and cervical dysplasia (10.1%). The AEs most frequently classified as severe were pelvic pain (2.3%), dysmenorrhea (1.9%), headache (1.7%) and abdominal pain (1.4%). A total of 328 subjects (22.6%) on LCS16 discontinued the study due to AE. The most frequent AEs leading to study discontinuation were vaginal hemorrhage (3.5%), device expulsion (3.0%), pelvic pain (3.0%) and acne (1.9%).

A total of 803 subjects (55.3%) treated with LCS16 had AEs that were considered as drug-related. Most frequent drug-related AEs were: ovarian cyst (15.7%), acne (10.2%), pelvic pain (6.3%), dysmenorrhea (5.4%) and vaginal hemorrhage (5.0%).

A total of 86 subjects (5.9%) experienced an SAE during the study and 19 subjects (1.3%) had at least 1 SAEs that was assessed as related to the study drug. Most frequent study drug-related SAEs were ectopic pregnancy in 7 subjects (0.5%) (in addition, there was 1 woman with a ruptured ectopic pregnancy, also an study drug-related SAE) and pelvic inflammatory disease in 5 subjects (0.3%). A total of 2 deaths occurred during the stud, both in the LCS16 group, one polytraumatisation due to a traffic accident and one suicide, both deaths were considered as unrelated to the study treatment.

From a total of 1452 subjects treated with LCS16, there were 8 subjects diagnosed with an investigator-confirmed PID. 5 of these cases occurred during the first year of use, 1 in the 3rd year and 2 in the 4th year. A total of 3 cases met the protocol-defined criteria for PID.

Other safety results, LCS12 and LCS16

A total of 3 partial uterine perforations were reported during the study, all in the LCS16 group. All of them were partial perforations of the myometrium (or myometrial embedment)

by the LCS. In all 3 cases, the IUS was removed via the vagina. The subjects recovered without sequelae.

No clinically meaningful changes in laboratory values or vital signs were seen among subjects in either treatment group during the first 3-years, or during the extension phase in the LCS16 group.

Dysmenorrhea, in terms of the number of subjects affected and in the number of days, decreased markedly over the first 3 years of treatment (in both treatment groups) by up to 75%. The biggest reduction was usually in the second month after insertion of the IUS, with a clear trend for further gradual reduction over 3 years. In the LCS16 group, a clear trend for further gradual reduction was seen over 5 years.

Overall, a total of 2990 insertion attempts (LCS12: 1481, LCS16: 1509; including first and second attempts) were performed, of which 96.0% (2871; LCS12: 1426, LCS16: 1445) were completed. In total, 2871 women had successful insertions (LCS12: 1426 women, LCS16: 1445 women). Of these, 2770 were successful at the first attempt and 101 were successful at the second attempt. Insertion failed in 13 women (LCS12: 6 women, LCS16: 7 women). Investigators assessed the insertion procedure as easy in 89.6% of the women (LCS12: 89.6%, LCS16: 89.7%), and most of the subjects experienced either no pain (19.5%; LCS12: 20.6%, LCS16: 18.5%) or considered the pain as mild in severity (45.5%; LCS12: 43.9%, LCS16: 47.0%). Nulliparous subjects experienced moderate or severe pain more often than parous subjects, but this is not judged to be a limiting factor in the use of LCS in nulliparous women, with the majority of these women (85.4% and 94.1%) experiencing no more than moderate pain during insertion and removal, respectively.

There was no decrease in mean bone mineral density measurements in either treatment group during the study indicating that concerns about a negative impact of LNG on skeletal heath should not affect the use of LCS by healthy women in the target population.

Pharmacokinetic (PK) evaluation

In a subgroup of 6 women a detailed model-independent pharmacokinetic evaluation has been accomplished. Of these 6 women, 3 continued in the extension phase until the end of the study after 5 years. Maximum LNG concentrations were observed within the first two weeks, with a high interindividual variability. This can be attributed to the higher early release rates during the first few weeks, due to the open ends of the LNG-containing elastomer core of LCS, which results in a faster dissolution into the surrounding medium right after insertion. Thereafter, the mean serum levels of LNG decreased slowly from average concentrations at 3 months of 100 ng/L and 157 ng/L (N=6) to average concentrations at 3 years of 59 ng/L and 108 ng/L (N=6) for LCS12 and LCS16, respectively, and to 74.2 ng/L (N=3) for LCS16 at 5 years.

A population PK model described the LNG serum concentrations after insertion of LCS12 and LCS16 in all subjects valid for analysis well. Based on this model, individual total and unbound LNG serum concentrations were estimated at selected times. In the LCS12 group (3-year data), the mean serum levels of total LNG decreased slowly from average concentrations at 1 month of 131 ng/L (N=1120), and 99.8 ng/L at 3 months (N=1093) to average concentration of 58.6 ng/L (N=248) at 3 years. In the LCS16 group (5-year data), the mean serum levels of total LNG decreased slowly from average concentrations at 1 month of

152 ng/L (N=1253) and 142 ng/L at 3 months (N=1223) to average concentrations at 3 years 0f 91.3 ng/L (N=774) and to 83.1 ng/L (N=224) at 5 years. The estimated values of the population PK analysis are similar to the measured values in the PK subgroup (N=3 or 6). The included covariate analysis revealed an effect of body weight on the clearance parameter (CL/F of LNG increases linearly by 0.84% per kg body weight).

Based on the population PK approach, the *in vivo* release rate of LCS12 was 11.6 µg/day at day 30, and declined to 6.21 µg/day at at year 1, and was 5.36 µg/day at the end of 3 years. The calculated averate release rate over the entire time of LCS12 use (3 years) was 6.4 µg/day. For LCS16 (5-year data), the *in vivo* release rate was 17.5 µg/day at day 25 and declined rapidly to 9.79 µg/day at 1 year and 7.89 µg/day at 3 years after insertion. Thereafter, the release rate remained relatively stable until the end of year 5 (7.44 µg/day). The calculated average release rate over the entire time of LCS16 use (5 years) was 8.99 µg/day. The higher release rate in the initial phase can be attributed to the open ends of the LNG-containing elastomer core of LCS.

Overall conclusions

In conclusion, the results of this study confirm the contraceptive efficacy of LCS12 and LCS16 up to 3 years, and the contraceptive efficacy of LCS16 for up to 5 years, and affirm the positive safety profile of LNG-releasing IUSs, with no new or unexpected findings. The benefits of treatment were demonstrated by the very low PIs and the favorable menstrual bleeding patterns, while the incidence of treatment related adverse events was low in both nulliparous and parous young women. The removal and insertion procedures were considered easy by the vast majority of this study population and their physicians. The adverse event profile, including the incidence of ectopic pregnancy, PID, perforation and expulsion are in line with the current body of knowledge for LNG releasing IUSs and IUDs in general.

Product Identification Information

Product Type	Drug
US Brand/Trade Name(s)	Skyla
Brand/Trade Name(s) ex-US	Jaydess, Luadei, Fleree
Generic Name	Levonorgestrel
Main Product Company Code	BAY86-5028
Other Company Code(s)	
Chemical Description	Levonorgestrel: (-)-13-Ethyl-17-hydroxy-18,19-dinor-17alpha-pregn-4-en-20-yn-3-one
Other Product Aliases	LCS12, LCS16

Date of last Update/Change: 20 Feb 2013
Date disclosed via Websynopsis