Science For A Better Life

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.

Synopsis

Date of report:	11 FEB 2015
Study title:	Multicenter, randomized, open-label, parallel-group study to evaluate user satisfaction with and tolerability of the low-dose levonorgestrel (LNG) intrauterine delivery system (IUS) with 12 µg LNG/day initial in vitro release rate (LCS12) in comparison to a combined oral contraceptive containing 30 µg ethinyl estradiol and 3 mg drospirenone (Yasmin®) in young nulliparous and parous women (18-29 years) over 18 months of use
Sponsor's study number:	13362
NCT number:	NCT01254292
EudraCT number:	2010-020181-21
Sponsor:	Bayer
Clinical phase:	III

Study objectives:	The following were the overall objectives for this study: The primary objective of the study was to: • Evaluate user satisfaction in young nulliparous and parous women (18 to 29 years of age) using LCS12 compared with young nulliparous and parous women using a COC over a period of 18 months Secondary objectives were to: • Determine the tolerability, discontinuation rates, AE profiles, occurrences of unintended pregnancies (including calculation of PI), and bleeding profiles with the 2 birth-control methods The objectives of the extension phase of the study were to: • Determine the tolerability of LCS12, discontinuation rates, AE profiles, occurrences of unintended pregnancies (including calculation of PI), concomitant medication, frequency of IUS expulsions • Record ease of removal of the IUS (investigator's assessment) and pain during removal (subject's assessment) • Provide the results of the return-to-fertility data that were collected in women who discontinued the LCS12 treatment due to wish to become pregnant (follow-up of up to 12 months after discontinuation of treatment). Above parameters are reported for the LCS12 arm over the entire study.
Test drug:	Skyla (Levonorgestrel, BAY 86-5028)
Batch Number(s)	C10101
Name of active ingredient(s):	Levonorgestrel
Dose:	12 µg LNG/day initial in vitro release rate
Route of administration:	Intrauterine

Duration of treatment:	18 months, with an extension phase for LCS12 users electing to continue use of the LCS12 beyond the 18-month endpoint of the comparative phase of the study (ie, for up to 36 months[3 years])[1]
Reference drug:	None
Diagnosis and main criteria for inclusion:	Subjects were generally healthy women requesting contraception and between 18 and 29 years of age (inclusive) at Screening. *And* In the opinion of the Investigator, the subject was in (i) good health; (ii) without uterine conditions that would preempt insertion of LCS12; and (iii) without conditions/history that would contraindicate the use of an intrauterine device (IUD) Subject had normal or clinically insignificant cervical smear (ie, one that does not require further follow-up) at Screening or documented normal result within 6 months of Screening. Subjects with atypical squamous cells of undetermined significance (ASCUS) could have been included in the study if they had a Human Papilloma Virus (HPV) deoxyribonucleic acid (DNA) test that, according to the standards of the local laboratory, was negative for high-risk HPV Subject had regular (ie, endogenous cyclicity without hormonal contraceptive use) menstrual cycles (length of Cycle 21 to 35 days) as determined by subject's history Subject was willing and able to attend the scheduled study visits and to comply with the study procedures
Study design:	Multicenter, randomized, open-label, parallel-group study assessing user satisfaction with and tolerability of LCS12, against a reference COC (combined oral contraceptive). An optional 18-month extension phase of treatment was offered to the women in the LCS12 arm, bringing the total study time to 3 years. This report covers data captured during the 3-year period of LCS12 use.

[1] The extension phase for LCS12 users was added under Amendment 1. See Section 13.1, Modification 1.

Methodology	The primary efficacy variable - the overall satisfaction rate at the end of the comparative phase of the study (or at early termination for those subjects discontinuing the study before completion of the 18-month comparative phase)– was reported in the comparative phase (CSR PH-37261). Variables presented in this report include: • discontinuation rates, • safety/AE profiles • occurrences of unintended pregnancies (including calculation of PI) • frequency of IUS expulsions • removal ease (investigator's assessment) and pain (subject's assessment) • return to fertility data	
Study center(s):	42 investigational sites in 4 countries: Austria (10), Belgium (5), Germany (15) and USA (12)	
Publication(s) based on the study (references):	None	
Study period:	First subject, first visit:	06 JAN 2011
	Last subject, last visit:	28 MAY 2014
Early termination	No	
Number of subjects:	Planned:	275
	Analyzed:	282 randomized 279 treated (FAS) More details are given in the section on study subjects below.

Criteria for evaluation ***Efficacy / clinical pharmacology:***	Efficacy variables include: • discontinuation rates, • occurrences of unintended pregnancies (including calculation of PI) No pharmacokinetic (PK) / pharmacodynamic (PD) components were analyzed for this report. The residual content of LNG in used LCS12 was analyzed. LCS12s were collected from 80 subjects who prematurely discontinued or who completed the study between 13 days and 801 days (approximately 27 months) after insertion. These samples include 41 subjects who discontinued the study prematurely during the comparative phase, 24 subjects who completed the comparative phase and 15 subjects who discontinued during the extension phase of the study.
Safety:	All AEs recorded during the study were classified using MedDRA v. 17.0, summarized on the level of system organ class and preferred term, and by maximum intensity, causal relationship to study drug, causal relationship to study conduct, outcome and seriousness. The number of subjects discontinuing study treatment due to AEs are presented. SAEs are displayed separately.
Other:	Not applicable
Statistical methods:	All variables were analyzed descriptively
Substantial protocol changes:	**Protocol Amendment 01, dated 15 MAR 2011** The following major changes were adopted in Amendment 01: • Added an 18-month Extension Phase for subjects in the LCS12 treatment group • Changed time point of Interim Analysis from after completion of Visit 2 to after completion of Visit 3 to allow inclusion of 1 month safety data • Modified Exclusion Criteria as follows: o Updated Criterion #1 to reflect current clinical practice regarding pregnancy o Removed Criterion regarding history of ectopic pregnancy o Clarified Criterion #7 to state that exclusion of subjects for PID applied only to acute, current or

recurrent forms of the disease

- Modified Criterion #13 regarding "clinically significant" ovarian cysts to indicate that this assessment is based on the investigator's clinical judgment
- Removed criterion regarding the prior use of IUDs or IUSs within Visit 1 as the protocol now provides specific instructions regarding subjects switching to study drug from other forms of contraception
- Clarified Criterion #27 regarding use of additional sex steroids and other drugs impairing ovarian function within 28 days of initiation of study treatment

- Modified timing of Visit 2 and switching of subjects from other forms of contraception
- Modified the protocol in response to requests from German Health Authority, to state that in Germany, only a gynaecologist may (1) insert the LCS12 and (2) perform gynaecologic investigations and procedures required by the study protocol
- Modified Section on withdrawal of subjects from the study to state that subjects experiencing new-onset of migraine with neurological symptoms, thromboembolic diseases during study treatment, icterus or pronounced increase in blood pressured MUST be withdrawn from treatment
- Changed the size of ovarian cysts to be reported as AEs from 5 cm to >3 cm
- Discontinued collection of dysmenorrhea data in the subjects' diaries
- Made minor clarifications and adjustments

Protocol Amendment 02, dated 22 JUL 2011

The following major changes were adopted in Amendment 02:

- Clarified the primary endpoint to state that this endpoint was to be assessed at the end of the Comparative Phase of the study.
- Clarified Safety Follow-up and EOS assessments for subjects who prematurely discontinued the study

- Added additional language regarding the need to discuss the use of back-up contraception for LCS12 subjects in preparation for the removal of the LCS12 and for COC subjects before Visit 6
- Clarified protocol to ensure that all pregnancies occurring during the study were appropriately reported to the sponsor, not only those occurring while study drug was being used
  - Clarified also that pregnancies occurring after the subject had stopped use of the study drug (ie, pregnancies identified at the 3-month or 12-month follow-ups for return to fertility) were to be reported to the sponsor using the appropriate form provided by the sponsor
  - Added specific language for LCS12 subjects who became pregnant indicating these subjects were to be followed until final outcome of the pregnancy
- Modified the protocol to indicate that the final clinical study report was not to include the results for the assessment of return to fertility as these data would not be available at the time of database closure
- Corrected inconsistent information in the protocol regarding the time allowed between the Screening Visit and Treatment-assignment Visit
- Changed definition of a compliant cycle in the COC group to indicate that no tablet could be forgotten on Cycle Days 1 through 21 and that the cycle length was to be no more than 28 days
- Made additional minor changes

Study subjects

A total of 644 subjects were screened of which 77 were screen failures and 567 were randomized, approximately 1:1 as follows: 282 subjects to LCS12 and 285 subjects to Yasmin. Of the 282 subjects randomized to LCS12, 279 (FAS) had an insertion attempt; 3 LCS12 subjects were never administered the study treatment i.e. did not have an insertion attempt and were discontinued from the study for the following reasons: protocol violation (subject 140060015) and withdrawal of consent (subjects 280050006 and 440070001).

A total of 55 (19.5%) subjects randomized to LCS12 prematurely discontinued the 18 months comparative phase study versus 81 (28.4%) subjects randomized to the Yasmin group who did not complete the study (CSR PH-37261). A total of 227 LCS12 subjects (80.5%) completed the 18-month comparative phase of the study, and 163 of 200 subjects (81.5%) that entered the 18-month LCS12 extension phase completed the entire 3-year study. Thirty-seven (18.5%) subjects prematurely discontinued the extension phase.

More than 90% (ie, 262 [93.9%]) of the subjects were white, 11 (3.9%) were black, 2 (0.7%) were Asian; 1 (0.4%) with race "not reported"; while 3 (1.1%) reported multiple races. More than 90% (ie, 267 [95.7%]) were not Hispanic or Latino. The mean±SD age was 23.7±3.0 years. Both the mean (23.9±4.3 kg/m^2) and median BMI (23.2, range 17.1 to 42.4 kg/m2) were <25 kg/m^2.

With respect to the frequency of alcohol use, most subjects 202 (72.4%) were light users. More than one-half of the subjects (166 [59.5%]) did not have a history of smoking, 27 (9.7%) were former smokers and 86 (30.8%) were current smokers.

More than one-half of the subjects (154 [55.2%]) had College or University Education; 104 (37.3%) had Secondary Education and 21 (7.5%) had Elementary Education.

Demographics were similar for both the subjects continuing in the extension and subjects who did not continue in the extension study.

More than two thirds of the subjects (73.1%) had never been pregnant; 26.8% had at least 1 pregnancy, 22.6% had given birth at least once, 16.6% had at least one vaginal delivery, and 7.5% had at least 1 cesarean birth). There were no subjects with a history of ectopic pregnancy.

More than 99% of the subjects – those that continued in the extension (200 [99.5%]) and those that did not continue (79 [100%]) - had regular menstrual cycles. The average length of the menstrual cycle in both groups was 28 days. The average duration of withdrawal/ menstrual bleeding was similar for both groups at 4.6 vs 4.7 days, respectively.

Only 1.8% had never used any contraceptives, 86.4% had prior use of oral hormonal contraception, 2.2% had prior use of IUS and 2.9% prior use of IUD. Contraceptive history was similar between the extension versus non-extension subjects.

The most commonly used prior medications included substances typically used by young, healthy women in need of contraception. Similarly, the most frequently used concomitant medications recorded over a treatment period of 3 years are considered typical of a study population of young, healthy and sexually active women. The high frequency of the concomitant use of ibuprofen and paracetamol includes their use as pain medication before and/or after the IUS insertion procedure. The practice of using misoprostol to facilitate IUS insertion procedures is reflected in this study, and was used in almost one third of the LCS12 subjects.

Efficacy / clinical pharmacology evaluation

- The cumulative drop-out rate by the end of the 3-year study was 33.3% reflecting high continuation rate with LCS12, and being in line with the earlier conducted LCS12 studies.
- The contraceptive efficacy of LCS12 was good with an unadjusted overall PI of 0.65 (95% CI: 0.18 - 1.67) and highest PI 0.83 (95% CI: 0.10 - 2.99) observed in the first year. The confidence intervals overlap with the corresponding CIs (overall PI 95% CI: 0.16 – 0.60; 1st year PI 95% CI: 0.13 – 0.96) of those obtained from the pivotal study A52238. It should be noted that this study was too small for a precise estimation of the Pearl Index, as demonstrated by the wide confidence intervals.
- The expulsion rate was very low, of 279 women studied, only 1 subject (0.4%) experienced an IUS expulsion (partial).
- Removals were easy in over 90% of the cases and with either no or only mild pain in almost 90% of the cases.
- Residual LNG content was between a maximum of 14.2 mg shortly after insertion and a minimum of 9.5 mg after 801 days and declined steadily over time. These data are very well in accordance with previous residual content measurements.

Safety evaluation

- LCS12 was well tolerated. No new or unexpected AEs were observed. More than three quarters of subjects (228 [81.7%]) experienced at least 1 TEAE. For most subjects who experienced TEAEs, these AEs were either mild or moderate. A total of 47 subjects (16.8%) experienced treatment-emergent AEs of severe intensity. Approximately 39% of the subjects (108) experienced at least 1 study drug-related TEAE. Twenty-seven subjects (9.7%) experienced at least one protocol required procedure-related AE.
- A total of 188 (67.4%) women reported at least 1 TEAE during the first year of this study, 122 (50.6%) during the second year and 66 (35.7%) during the third year of the study. A decreasing trend was seen amongst most of the TEAE parameters with each successive year.
- No subject died and 22 (7.9%) subjects experienced at least 1 TEAE determined by the Investigator to be an SAE; 4 SAEs were considered to be treatment related SAEs; (LCS12 was withdrawn in 3 of these cases - ectopic pregnancy (100080017; 280020005) and spontaneous abortion (280040042).
- Thirty-eight (13.6%) subjects experienced at least 1 AE leading to discontinuation and seven subjects (2.5%) experienced an SAE that led to discontinuation of study drug. A total of 28 subjects (10.0%) experienced at least 1 study drug related AE that led to discontinuation of study drug.
- A total of 27 subjects (9.7%) experienced at least 1 AE related to procedures required by the protocol. The most frequent study procedure-related AEs were in 3 or more

subjects were: lower abdominal pain 4 (1.4%), abdominal pain, procedural pain and pelvic pain each in 3 (1.1%) subjects. Also recorded were: presyncope in 2 (0.7%) subjects and syncope in 1 (0.4%) subject.

- In total, 20 ovarian cysts and 4 ruptured ovarian cysts were reported among LCS12 subjects. None of the ovarian cysts led to discontinuation.
- There were four cases in the LCS12 group where the Pelvic Inflammatory Disease (PID) Form was completed. None of these 4 cases met the criteria for the diagnosis of PID, as stipulated in the protocol.
- In total, 1 device expulsion and 1 (intra-uterine) device dislocation (location of the IUS was confirmed by ultrasound to be *in situ* and this case was therefore not reported as partial expulsion) were reported during the study.
- Four out of 279 women in the LCS12 arm had unintended pregnancies during the study. Three of the 4 pregnancies that occurred during the study treatment were ectopic, 2 of them in nulliparous and 1 in a parous subject. The one intrauterine pregnancy was in a nulliparous subject and ended in a spontaneous abortion.
- The observed rates for return to fertility are consistent with the fertility rates observed after discontinuation of an intrauterine system (IUS) with LNG and with those in non-contracepting women with comparable demographic profiles.

Overall conclusions

The results of this 3-year safety and efficacy study of LCS12 in young nulliparous and parous women showed that LCS12 was well tolerated and highly effective over the entire period of use up to 3 years. No new or unexpected AEs were observed. For most subjects who experienced TEAEs, these AEs were either mild or moderate. The unadjusted overall PI was 0.65 (95% CI: 0.18 - 1.67); the highest PI 0.83 (95% CI: 0.10 - 2.99) was observed in the first year. The wide CIs for the PIs in this study overlap with the pivotal contraceptive efficacy and safety study with LCS12. In total, 200 women out of 227 who completed the comparative phase of this study, chose to continue to the voluntary 18 month extension phase. This is indicative of high acceptability and high satisfaction with the use of the LCS12. The cumulative drop-out rate by the end of the 3-year study was 33.3% reflecting high continuation rates with LCS12, and in line with earlier conducted LCS12 studies. The observed rates for return to fertility are consistent with the fertility rates observed after discontinuation of an intrauterine system (IUS) with LNG and with those in non-contracepting women with comparable demographic profiles.

LCS12 was proven safe and effective during the 3 year period of use and the results of this study are in line with the data observed in previously conducted studies with LCS12.

Investigational Site List

Marketing Authorization Holder in Germany	
Name	Bayer Vital GmbH
Postal Address	D-51368 Leverkusen Germany
Sponsor in Germany (if applicable)	
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Product Identification Information

Product Type	Drug
US Brand/Trade Name(s)	Skyla
Brand/Trade Name(s) ex-US	Jaydess, Luadei, Fleree, Janess
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

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