Clinical Study Synopsis

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The study listed may include approved and non-approved formulations or treatment regimens. Data may differ from published or presented data and are a reflection of the limited information provided here. The results from a single trial need to be considered in the context of the totality of the available clinical research results for a drug. The results from a single study may not reflect the overall results for a drug.

Bayer HealthCare

Clinical Trial Results Synopsis

Study Design Description		
Study Sponsor:	Bayer Healthcare AG	
Study Number:	91412	NCT00185380
Study Phase:	II	
Official Study Title:	Multi-center, open, randomized, dose finding phase II study to investigate for a maximum of three years ultra low dose levonorgestrel contraceptive intrauterine systems (LCS) releasing in vitro 12 µg/24 h and 16 µg/24 h of levonorgestrel compared to MIRENA in nulliparous and parous women in need of contraception	
Therapeutic Area:	Women's Healthcare If 'Other', please specify:	
Test Product		
Name of Test Product:	Other If 'Other', please specify: Ultra-low dose levonorgestrel contraceptive intrauterine systems (BAY86-5028)	
Name of Active Ingredient:	Levonorgestrel (LNG)	
Dose and Mode of Administration:	Intrauterine system (IUS) with 2 dose groups: initial in vitro release: 12 µg LNG/24 h and 16 µg LNG/24 h	
Reference Therapy/Placebo		
Reference Therapy:	Mirena IUS	
Dose and Mode of Administration:	IUS with initial in vitro release: 20 µg LNG/24 h	
Duration of Treatment:	Up to 3 years	
Studied period:	**Date of first subject's first visit:**	19 Apr 2005
	Date of last subject's last visit:	09 Dec 2008

Study Center(s):	37 centers in 5 countries: Finland (16 centers), Sweden (8 centers), Norway (6 centers), Hungary (4 centers) and the UK (3 centers)
Methodology:	This was a multi-center, randomized, 3-arm, parallel group phase II dose-finding study. Two doses of intrauterine administered LNG (initial in-vitro release 12 µg and 16 µg LNG per day) were studied and compared to Mirena (initial in-vitro release 20 µg LNG per day). Subjects were to keep the IUS for 3 years. Yearly interim efficacy analyses were to be performed (Pearl Index) and a treatment arm was to be stopped if lack of efficacy was observed.
Indication/ Main Inclusion Criteria:	Parous or nulliparous women of 21 to 40 years of age (inclusive) with good general health and in need of contraception
Study Objectives:	**Overall:** To search for an appropriate LNG dose for a new contraceptive IUS suitable for use by nulliparous and parous women.
Evaluation Criteria:	**Efficacy (Primary):** Number of unintended pregnancies (Pearl Index) **Efficacy (Secondary):** Bleeding patterns by 90-day reference periods **Safety:** Adverse events, clinical laboratory examination, vital signs, endometrial examination (vaginal ultrasound), **Other:** Number of IUS expulsions, ease and pain of IUS insertion and removal

Statistical Methods:	**Efficacy (Primary) - if applicable:** Pearl Index for pregnancies **Efficacy (Secondary) - if applicable:** Descriptive statistics **Safety:** Descriptive statistics **Other - if applicable:** Number of partial or total IUS expulsions, descriptive statistics of IUS insertion and removal ease and pain.
Number of Subjects:	Planned: 690 (230 per dose group) Analyzed: 738 (LCS12: 239, LCS16: 245, Mirena: 254)

Study Results

Results Summary — Subject Disposition and Baseline

The women in the study were between 20 and 41 years of age, in good general health, and in need of contraception. A total of 905 women were screened, leading to a total of 742 who were randomized and 738 who had an IUS inserted (LCS12: 239, LCS16: 245, Mirena: 254). The 738 women treated were included in the full analysis set (FAS), which was identical to the per protocol analysis set (PPS) and used for the efficacy and safety analyses. There were no major protocol deviations. A total of 208 women (28.2%; treatment groups comparable) discontinued study medication prematurely.

The majority of women (733/738) in the FAS were Caucasian. The mean age of the subjects was approx. 32 years (32.1 [SD 5.31]). The three treatment groups were comparable with respect to demographic and baseline characteristics. Of the 738 women in the FAS, a total of 159 (21.5%) were nulliparous, and 579 (78.5%) had had one or more births. A total of 538 (72.8%) women had had at least one vaginal delivery. The treatment groups were comparable with regard to gynecological history.

Results Summary — Efficacy

A total of 6 pregnancies were observed under treatment; 1 in the LCS12 group (an ectopic pregnancy) and 5 in the LCS16 group (of which 2 were ectopic). Of the remaining 3 pregnancies, 2 ended in spontaneous abortion and 1 pregnancy was normal and carried to term (the result of an un-noticed expulsion). The pregnancy in the LCS12 group occurred in the second year of treatment, and of the 5 pregnancies in the LCS16 group, 1 occurred in the first year of treatment, 3 in the second year of treatment and 1 in the third year of treatment. The total exposure in woman years (WY) was comparable in the three treatment groups: LCS12: 601.68 WY, LCS16: 611.48 WY, Mirena: 627.94 WY.

The adjusted and unadjusted 3-year Pearl Indices (PI) were identical (LCS12: 0.17, LCS16: 0.83, Mirena: 0). The upper limits of the 95% confidence interval were below 2 for all 3 treatment groups. No clear dose-response relationship was observed, since more pregnancies occurred in the LCS16 group than in the LCS12 group, and no pregnancies occurred in the Mirena group. No pattern in the pregnancy rates over time was observed. Although exposure was comparable in Years 2 and 3, most pregnancies (LCS12: 1, LCS16: 3) occurred in Year 2, and only 1 occurred in Year 3 (LCS16), indicating a contraceptive effect for the whole treatment period of 3 years.

In general, the biggest decrease in the mean number of bleeding and spotting days occurred between the first and second 90-day reference periods. Since IUS insertion was scheduled during bleeding, the more meaningful observation starts with the second reference period. By the third reference period, bleeding and spotting had decreased considerably. Bleeding and spotting then continued to decrease gradually over the 3-year study period, with few fluctuations. The mean results are summarized in Table 1.

Table 1: Descriptive statistics of bleeding/spotting by 90-day reference periods

	Bleeding/ spotting days	Bleeding days	Spotting only days	Bleeding/ spotting episodes	Spotting only episodes
LCS12					
Ref. period 1	39.9	15.1	24.8	3.9	1.6
Ref. period 2	22.6	8.2	14.4	3.7	1.7
Ref. period 3	18.3	6.4	12.0	3.2	1.6
Ref. period 4	16.7	5.5	11.2	3.2	1.5
Ref. period 12	12.8	3.6	9.2	2.6	1.5
LCS16					
Ref. period 1	39.2	15.4	23.8	3.8	1.8
Ref. period 2	21.8	7.7	14.1	3.4	1.6
Ref. period 3	16.7	5.4	11.3	3.0	1.6
Ref. period 4	15.0	4.7	10.2	2.9	1.5
Ref. period 12	10.6	3.0	7.7	2.4	1.3
Mirena					
Ref. period 1	36.6	14.3	22.2	3.3	1.6
Ref. period 2	21.8	7.6	14.2	3.2	1.7
Ref. period 3	16.8	5.3	11.5	2.9	1.6
Ref. period 4	15.2	4.2	11.0	3.0	1.9
Ref. period 12	8.8	1.9	6.9	2.3	1.5

Results Summary — Safety

A total of 660 women (89.4%) reported at least 1 AE during the study. A total of 4000 events were reported in all. More women (over 80%) reported AEs during the first year of treatment than in the second and third years (a little over 50%). The reporting of AEs was comparable across the treatment groups. AEs were reported most frequently in the system organ classes reproductive system and breast disorders: 399 women (54.1%), infections and infestations: 357 women (48.4%), gastrointestinal disorders: 280 women (37.9%), skin and subcutaneous tissue disorders: 264 women (35.8%), nervous system disorders: 240 women (32.5%), and psychiatric disorders: 170 women (23.0%).

Common AEs (occurring in >5% of subjects in any treatment group) were various but most occurred in <10% of the study population. The most common AEs overall were headache (28.2%), acne (26.8%), breast discomfort (22.4%), abdominal distension (18.8%), mood altered (15.0%), ovarian cyst (14.8%), weight increased (14.6%), breast pain (11.1%) and vulvovaginal candidiasis (10.0%). The treatment groups were comparable with regard to the most common AEs. Events that occurred more frequently in the Mirena group than the LCS groups with a difference in frequency of >5% were headache (32.3% vs. 26.4% and 25.7%) and ovarian cyst (25.2% vs 8.8% and 9.8%). Events that occurred more frequently in one of the LCS groups than the other with a difference in frequency of >5% were mood altered (LCS12: 18.0% vs LCS16: 12.2%, Mirena: 15.0%) and breast pain (LCS12: 8.4% vs LCS16: 14.3%, Mirena: 10.6%).
A total of 106 women (14.4%) reported AEs that were rated by the investigator as severe in intensity. For 385 women (52.2%) the maximum intensity was moderate, and for 163 women (22.1%) the maximum intensity of AEs was mild. The distribution of women with mild, moderate and severe events was approximately equal among the treatment groups. The AEs most frequently classified as severe were dysmenorrhea (13 women), abdominal pain (9 women), and lower abdominal pain and procedural pain (7 women each). All other AEs of severe intensity were reported in very few women per treatment group.
A total of 509 women (69.0%) experienced at least 1 AE related to LCS or Mirena. The treatment groups were comparable with regard to drug-related AEs, with only slightly more (72.4%) women in the Mirena group than in the LCS groups (67.8% and 66.5%) with drug-related AEs. The only drug-related AE that occurred considerably more often in any treatment group was ovarian cyst, which was reported for 56 women (22.0%) in the Mirena group, compared with 14 women (5.9%) in the LCS12 group and 21 women (8.6%) in the LCS16 group. This difference is plausible, as the lowest systemic exposure to LNG in the LCS12 treatment group did not lead to a suppression of ovulation, in contrast to what was observed in the Mirena group. No relevant differences among the treatment groups or over time were seen for any individual progestin-related side-effects, although there was a general trend towards fewer such side effects later in the study.
No deaths were reported. No partial or complete perforations were reported. One woman (LCS12) had a malignant melanoma that was excised and the woman recovered. Two women (LCS16:1, Mirena: 1) showed symptoms of pelvic inflammatory disease, were treated, and recovered. The 63 SAEs reported in 40 women were distributed over the 3 treatment groups, with a slightly higher percentage of women in the Mirena group reporting SAEs than in the LCS groups (LCS12: 5.0%, LCS16: 4.9%, Mirena: 6.3%). The occurrence of ovarian cysts was more pronounced in the Mirena group, with 5 women reporting SAEs, compared with only 1 woman in the LCS 12 group and none in the LCS16 group. All women recovered from these events.

SAEs in 10 women were reported by the investigator to be related to study drug, and in 5 of these cases study drug was withdrawn (due to ovarian cyst in 2 women in the Mirena group, ectopic pregnancy in 1 woman each in the LCS12 and LCS16 groups, and acute, severe vaginal bleeding in 1 woman in the Mirena group). The other related SAEs were adhesiolysis (in 1 woman in the LCS12 group), ectopic pregnancy, spontaneous abortion (each in 1 woman in the LCS16 group; IUS also removed shortly afterwards) and ovarian cyst (2 women in the Mirena group). Study drug was also withdrawn as a result of 2 further SAEs (unrelated), both in the LCS16 group, due to pelvic inflammatory disease (assessed by the investigator as related to the study procedure) and pregnancy. A total of 169/4000 AEs (4.2%) in 136 women led to the study treatment being withdrawn (LCS12: 42, LCS16: 46, Mirena: 48). A total of 116/738 women (15.7%) had AEs that were thought to be related to study treatment and that led to withdrawal. The preferred terms of the related AEs most frequently leading to withdrawal of study treatment (>1.0%) were acne, vaginal hemorrhage, mood altered, abdominal pain and ovarian cyst.The treatment groups were affected similarly, with acne affecting more women in the Mirena group than the LCS groups (LCS12: 6, LCS16: 7, Mirena: 14), but overall the numbers of women were small.

The majority of women had normal laboratory values at screening (93.8%) and at end of study (96.7%). Abnormalities were distributed evenly among the treatment groups. Laboratory abnormalities that occurred in >10% of women in any treatment group were gamma-GT, triglycerides, total cholesterol and HDL cholesterol. Although individual clinically relevant abnormalities were generally of unclear etiology, there were no relevant differences among the treatment groups or trends over time in the incidence of treatment-emergent abnormalities in any laboratory parameter.

No relevant differences in vital signs were noted among treatment groups or over time.

No more than 1 or 2 women had abnormal endometrial findings at any vaginal ultrasound examination. The maximum number of abnormal findings were at end of study (2 women each in the LCS16 and Mirena groups). No differences were noted among the treatment groups or over time in the number or type of fibroids demonstrable by ultrasound. Slightly more women in the Mirena group than in the LCS groups had ovarian abnormalities seen by ultrasound, especially at Months 6 and 12 and more ovarian cysts occurred in the Mirena group than in the two LCS groups. Epithelial cell abnormalities were seen in 4/738 cervical smears (0.5%) at screening and 28/738 cervical smears (3.8%) at end of study. The treatment groups were comparable.

Results Summary — Other

There were 3 total expulsions of the IUS (all in the LCS16 group) and 7 partial expulsions (LCS12: 1, LCS16: 2, Mirena: 4). Expulsions occurred at various times during the study treatment period with no trend detectable.

Insertion of the IUS failed in 4 women (LCS12: 1, LCS16:1, Mirena: 2). In most of the 738 women with successful insertions, insertion of the IUS was achieved at the first attempt (727 women); a second attempt was necessary in only 11 women. The investigator assessed the whole IUS insertion procedure as easy in 226/239 women (94.6%) in the LCS12 group and in 229/245 women (93.5%) in the LCS16 group. In the Mirena group the proportion of easy insertions was smaller (219 women; 86.2%). The investigators' evaluation of the insertion procedure was also analyzed by parity. Insertion in parous women was easier in all treatment groups, while in nulliparous women there was a trend towards easier insertion of an LCS than a Mirena. Women in the LCS groups generally experienced less pain than those in the Mirena group. Over 72% of women in the LCS groups experienced no pain or only mild pain during insertion of the IUS, compared with 57.9% in the Mirena group. Approximately 23% of women in the LCS groups and 35.4% in the Mirena group experienced moderate pain, and approximately 4.3% of women in the LCS groups and 6.7% in the Mirena group experienced severe pain.
The removal of the IUS was assessed by the investigators as easy in 499/738 women (68.1%). Of the 12 women in whom removal was assessed as very difficult, 7 were in the LCS12 group and 5 were in the LCS16 group. The investigators' general assessment of the removal procedure was missing for over 70% of the women in the Mirena group, because many women chose to keep the Mirena after the end of the study (in accordance with the terms of the protocol). Hence a comparison of the groups was not possible. Over half of the women in the study (458/738; 62.5%) experienced no or only mild pain on removal of the IUS. In total 61 women (8.3%) reported moderate pain and 23 women (3.1%) severe pain. However, since the subjects' evaluation of pain was missing or not available for over 70% of women in the Mirena group, no comparison of the groups was possible.

Conclusion(s)	
Both LCS groups showed low PIs and acceptable bleeding profiles. The removal and insertion procedures were considered easy by the vast majority of women and their physicians, and the pattern of adverse events was as expected. In nulliparous women there was a trend towards easier and less painful insertion of an LCS than a Mirena.	
Publication(s):	Gemzell-Danielsson K, Schellschmidt I, Apter D. A randomized, phase II study describing the efficacy, bleeding profile, and safety of two low-dose levonorgestrel-releasing intrauterine contraceptive systems and Mirena. Fertil Steril. 2012 Mar;97(3):616-22.e1-3. Epub 2012 Jan 4.
Date Created or Date Last Updated:	21 May 2012

Product Identification Information

Product Type	Drug
US Brand/Trade Name(s)	Mirena
Brand/Trade Name(s) ex-US	Mirena LNG
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	

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