Clinical Study Synopsis

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Bayer HealthCare

Clinical Trial Results Synopsis

Study Design Description		
Study Sponsor:	Bayer Healthcare AG	
Study Number:	91473 (309988)	NCT00393198 EudraCT number: 2006-000394-30
Study Phase:	IV Interventional	
Official Study Title:	Multicenter study to investigate the bleeding profile and the insertion easiness in women inserted with a second consecutive MIRENA for contraception or menorrhagia	
Therapeutic Area:	Women's Healthcare	
Test Product		
Name of Test Product:	Levonorgestrel IUD (Mirena, BAY86-5028) In the substudy as pretreatment: Cytotec tablet (misoprostol)	
Name of Active Ingredient:	Levonorgestrel Subset: misoprostol	
Dose and Mode of Administration:	MIRENA: in vitro release rate 20 micrograms LNG / 24 hours Cytotec in the substudy: 400 µg misoprostol, sublingual, 3 hours prior to the MIRENA removal and insertion procedure at entry visit	
Reference Therapy/Placebo		
Reference Therapy:	None in the main study. In the substudy: placebo tablet.	
Dose and Mode of Administration:	Substudy: single dose, sublingual, 3 hours prior to the MIRENA removal and insertion procedure at entry visit	
Duration of Treatment:	MIRENA: 5 years and 3 months Substudy: single application	
Studied period:	**Date of first subjects' first visit:**	03 OCT 2006
	Date of last subjects' last visit:	18 OCT 2012
Premature Study Suspension / Termination:	Not applicable	
Substantial Study Protocol Amendments:	Amendment 1 dated 01 NOV 2007, was globally implemented; it specified the following modifications: • The extension of the study duration from 1 year to 5 years • Changes to the visit schedule to accommodate the extension • Unblinding after 1 year in order to analyze the misoprostol substudy • Changes in the reporting plans to reflect the extension	

	• The addition of new case record forms and bleeding diary pages for the extension period • Updated subject information and informed consent form
Study Centre(s):	17 investigational sites treated subjects in 4 countries: 6 centers in Finland, 6 centers in France, 2 in Ireland and 3 in Sweden.
Methodology:	The study treatment was MIRENA, a LNG IUS with an initial in vitro release rate 20 μg LNG / 24 hours. The total study period was 5 years and 3 months, including a 3-month run-in prior to the removal of the first MIRENA and insertion of the second MIRENA, and 5 years of follow-up after the insertion of the second MIRENA. Primary efficacy variable of the study was the assessment of the bleeding pattern. Bleeding pattern were evaluated for the last 3 months of the first MIRENA use (baseline reference period), for the first year of the second MIRENA use, and annually for 90-day periods during Year 2 to Year 5.
Indication/ Main Inclusion Criteria:	Indication: contraception or menorrhagia • Women of 23 to 45 years of age (inclusive) who had already been using MIRENA for contraception or menorrhagia for between 4 years 3 months and 4 years 9 months and who were willing to continue with the method. • Normal size uterus at insertion, corresponding to ultrasound measure of 6 - 10 cm. • Clinically normal cervical smear result within 12 preceding months or at screening. • Clinically normal breast examination findings. For women ≥40 years at screening, a clinically normal mammography result within the preceding 12 months or at screening was required.
Study Objectives:	**Primary:** To assess the bleeding profile during the first year of use of the second consecutive MIRENA, and over the 5 years of use of the second consecutive MIRENA. **Secondary:** The assessment (by investigator and patient) of the removal of the first MIRENA and the insertion of the second MIRENA, continuation rate, menstrual comfort, and user satisfaction during 5 year of used. In a subset of women, the effect of sublingual misoprostol administration on the MIRENA insertion was evaluated by means of a nested-randomized, double-blind, placebo-controlled, comparative study in selected study sites in Finland and Sweden.

Evaluation Criteria:	**Efficacy (Primary):** The assessment of occurrence and intensity of bleeding during the last 3 months of use of the first MIRENA and the first year of use of the second MIRENA use. In addition, the occurrence and intensity of bleeding was evaluated during a 90-day period at end of each treatment year thereafter (i.e. Years 2, 3, 4, and 5). **Efficacy (Secondary):** Assessment of the removal of the first MIRENA and insertion of the second MIRENA (by investigator and subject). The removal and insertion were to be analyzed separately in the main study and in the substudy. In addition: continuation rate during the 5 years of use of the second MIRENA, pregnancy rate (Pearl Index), and expulsion rate. **Safety:** Adverse events, body weight, breast palpation, gynecological examination, and cytological (cervical) smear **Other:** Menstrual comfort and user satisfaction
Statistical Methods:	**Efficacy (Primary):** Bleeding pattern by descriptive statistics. **Efficacy (Secondary):** Continuation rate, menstrual comfort, and user satisfaction are presented by descriptive statistics, percentage of easy insertions analyzed by Fischer's exact test **Safety:** Safety parameters are presented by descriptive statistics.
Number of Subjects:	Planned: 200 subjects in total. Misoprostol substudy: minimum of 86 women in selected study centers in Finland and Sweden. Analyzed: 204 subjects (full analysis set); 170 subjects (full analysis set for the extension period).

Study Results

Results Summary — Subject Disposition and Baseline

A total of 234 Caucasian subjects were enrolled in this study. In the FAS, the total exposure time was 301,150 days corresponding to 824.5 woman years. To evaluate the effect of misoprostol or placebo on insertion easiness, a subgroup of 89 women were given a single dose of misoprostol (43 women) or placebo (46 women) shortly before the insertion procedure.

Following successful MIRENA insertion, 204 subjects started the first year of the study.
13 subjects discontinued the first year of treatment prematurely and another 21 subjects completed the study at Year 1 without continuing into the extension. .

A total of 170 subjects (mean ± standard deviation age: 38.7 ± 4.5 years) agreed to participate in the extension period. 26 subjects discontinued the extension period prematurely and another 144 subjects completed the extension period at Year 5.

All 170 subjects who participated in the extension period formed the FAS for the extension period.

The FAS for the extension period (n=170) was the relevant set for efficacy analyses, whereas the FAS (n=204) was the relevant set for safety analyses.

Summary of demographic and baseline characteristics in all women (FAS) is given in Table 1. In the pretreatment substudy, the two treatment groups were comparable with respect to demographic and baseline characteristics, including body weight, height, BMI and smoking history.

Table 1. Summary of demographic and baseline characteristics of all women - FAS

Variable	Total (N = 204)
Mean age (years [range])	38.7 [23-45]
Caucasian (n [%])	204 (100.0%)
Mean weight (kg)	67.1
Mean height (cm)	166.5
Body mass index (kg/m^2)	24.22
History of Smoking (n [%])	75 (36.8%)
If yes, current smoker	36 (48.0%)

Results Summary — Efficacy

Primary efficacy variable

In the FAS for the extension period, the mean number of bleeding / spotting days in reference period -1 (i.e. during the last 3 months of use of the first MIRENA) was 8.7 days. In reference period 1 of Year 1 (immediately after insertion of the second MIRENA), the mean increased to 11.9 days, in reference period 2, it decreased to 6.9 days, i.e. below the baseline value in reference period -1, and decreased further throughout Year 1. In reference periods 4 of Year 2 to Year 5, the mean number of bleeding / spotting days was 5.1 to 5.8 days, i.e. it remained at or below the level of bleeding / spotting days in reference periods 2 to 4 of Year 1.

The mean number of bleeding days (excluding spotting days) in reference period -1 was 2.7 days. In reference period 1 of Year 1, the mean increased to 3.4 days, in reference period 2, it decreased to 1.4 days, i.e. below the baseline value in reference period -1, and remained at that level throughout Year 1. In reference periods 4 of Year 2 to Year 5, the mean number of bleeding days was 1.6 to 1.8 days, i.e. it remained approximately at the level of bleeding days in reference periods 2 to 4 of Year 1.

The mean number of spotting only days in reference period -1 was 6.0 days. In reference period 1 of Year 1, the mean increased to 8.5 days, in reference period 2, it decreased to 5.4 days, i.e. below the baseline value in reference period -1, and decreased further throughout Year 1. In reference periods 4 of Year 2 to Year 5, the mean number of spotting only days was 3.6 to 4.1 days, i.e. it remained approximately at or below the level of spotting only days in reference periods 2 to 4 of Year 1.

Secondary efficacy variables

Insertion and removal of MIRENA. Misoprostol substudy: The removal of the first MIRENA was assessed by the investigators as easy in 194/204 women (95.1%). Of the 10 women in whom removal was assessed as difficult, 4 received no pretreatment, 3 received misoprostol and 3 received placebo. Nearly half of the women in the study (95/204; 46.6%) experienced no pain on removal of the first Mirena, and 81/204 (39.7%) experienced only mild pain. The women who received Misoprostol or placebo pretreatment did not experience less pain.

In total 203/204 women (99.5%) had a second MIRENA inserted. In most women (199/204)

insertion was completed at the first attempt; in 4 women at the second attempt. Only 1 woman (no pretreatment) did not have a second MIRENA inserted, due to retroversion of the uterus and technical problems. The investigator assessed the whole insertion procedure of the second MIRENA as easy in 182/204 women (89.2%). The investigator's assessment was 'easy' in 40/43 women (93.0%) in the misoprostol group and in 42/46 women (91.3%) in the placebo group. The proportions of easy insertions were compared using the two-sided Fisher's exact test, and the hypothesis "proportion of easy insertions with placebo ≥ proportion of easy insertions with misoprostol" could not be rejected (p=1.00). Approximately half of the women in the study (103/204; 50.5%) experienced no pain or only mild pain during the insertion of the second MIRENA. A total of 78/204 (38.2%) experienced moderate pain and 23/204 (11.3%) experienced severe pain. The women who received Misoprostol or placebo pretreatment did not experience less pain.

No apparent difference was seen in levels of pain experienced on insertion of the first and second MIRENA. The women who received Misoprostol or placebo pretreatment did not necessarily experience less pain that at the previous insertion.

The investigator assessed the removal of the second MIRENA as easy in 157/161 subjects (97.5%). In 4 subjects (2.5%), removal was assessed as difficult. In 1 subject, difficult removal was related to the MIRENA threads, which were not visible.

The continuation rate was very high. The Kaplan-Meier estimate of time to removal of the second MIRENA was 0.98 at Month 3. There were no partial or total expulsions of MIRENA in the first 3 months after insertion. The Kaplan-Meier estimates of time to partial expulsion and time to total expulsion of the second MIRENA were both 1.00 at Month 3. In total, 191/204 women (93.3%) continued using the second MIRENA for at least one year after insertion. The Kaplan-Meier estimate of time to removal of the second MIRENA was 0.94 at Month 12. There were no partial expulsions and only one total expulsion of MIRENA (expulsion after approx. 4 months). The Kaplan-Meier estimates of time to partial expulsion and time to total expulsion of the second MIRENA were both 1.00 at Month 12. Of 170 subjects who participated in the extension period, 26 subjects discontinued using MIRENA prematurely, i.e. 7 subjects experienced an adverse event, 5 were lost to follow-up and a further 3 had missing documentation, 3 withdrew their consent, 1 had a protocol deviation, 1 became pregnant, and 6 had other reasons.

Pregnancy rate. One subject, a 36-year-old woman, experienced incomplete spontaneous abortion approximately 24 months after insertion of the second MIRENA. Vacuum aspiration and removal of MIRENA were performed. In the FAS, the Pearl Index was 0.21 (95% confidence interval: 0.01 to 1.14) in subjects aged ≤40 years (486.7 woman years) and 0.0 (95% confidence interval: 0.00 to 1.09) in subjects aged >40 years (337.8 woman years).

Menstrual comfort. At Month 12, 76 women (39.2%) said that bleeding over the previous 12 months had decreased, compared with only 45 women (22.1%) at screening. At Month 12, bleeding had increased in only 8 women (4.1%) compared with 42 women (20.6%) at the screening visit. Almost all amenorrheic women (screening: 83 women, Month 12: 86 women) definitely agreed that they were satisfied with the absence of menstrual bleeding. Asked whether they were satisfied with their current menstrual bleeding pattern, 78 women (64.5%) definitely agreed at screening and 85 women (78.7%) definitely agreed at Month 12.

The percentage of subjects reporting decreased bleeding changed from 42.8% at Month 12 to a minimum of 10.2% at Year 4. This was accompanied by an increase of subjects who reported no change in bleeding (53.6% at Month 12 to a maximum of 77.6% at Year 4). The percentage of subjects who reported an increase in bleeding over the previous 12 months increased from 3.6% at Month 12 to 14.1% at Year 5 (EOS). However, this is due to the fact that the vast majority of subjects was amenorrheic or had spotting only – hence it was not possible that the bleeding would

have decreased further in those subjects.

Almost all amenorrheic subjects whose periods stopped during the use of MIRENA definitely agreed that they were satisfied with the absence of menstrual bleeding at all 5 annual time points after insertion of the second MIRENA. The maintenance of amenorrhea and the tendency towards reduced bleeding/spotting were regarded as key to the high degree of user satisfaction.

User satisfaction. The degree of user satisfaction was assessed in the three categories "not afraid of pregnancy, importance", "relief of daily intake, importance" and "satisfaction with study drug" at screening and annually, and with the additional category "continuation of study treatment" at Month 12 and Year 5. A large majority of women (approximately 95%) definitely agreed with the objects of satisfaction, at all 5 time points after insertion, with no notable differences between the visits.

Results Summary — Safety

In total, 167 of 204 subjects of the FAS (81.9%) experienced at least 1 treatment-emergent adverse event during the 5-year study period. 30 subjects (14.7%) experienced at least 1 treatment-emergent adverse event of severe intensity. 36 subjects (17.6%) experienced at least 1 adverse event considered related to MIRENA as assessed by the investigator. 7 subjects (3.4%) experienced 1 severe adverse event related to MIRENA. All other severe adverse events were not related to MIRENA. Adverse events in 87 of 167 subjects with treatment-emergent adverse events had resolved at study end and in 4 subjects, adverse events were resolving. In Year 1, 63.2% of the subjects experienced at least 1 treatment-emergent adverse event. In Year 2 to Year 5, this percentage of subjects decreased to a range of 31.0 to 49.1%.

During the entire 5-year study period, common individual treatment-emergent adverse events, i.e. adverse events which occurred in ≥5% of the subjects, were ovarian cyst (10.3%), cervical dysplasia (9.8%), headache (9.8%), vaginal infection (9.8%), sinusitis (8.8%), acne (7.8%), influenza (6.9%), back pain (6.4%), vulvovaginal candidiasis (6.4%), abdominal pain (5.9%), breast pain (5.9%), urinary tract infection (5.9%), and fungal infection (5.4%).

Out of the 20 subjects (9.8%) with 'cervical dysplasia' (preferred term), 17 (8.3%) were diagnosed with 'ASC-US' or 'atypical squamous cells of undetermined significance' ('ASC-US' means 'atypical squamous cells of undetermined significance' but both low level terms exist), 3 (1.5%) with 'LSIL' ('LSIL' means 'low-grade squamous intraepithelial lesion'), and 1 (0.5%) with 'cervical dysplasia' (all low level terms summarized as the preferred term 'cervical dysplasia').

There were no deaths during this study. 16 subjects experienced treatment-emergent serious adverse events. None of those events was assessed as related to MIRENA by the investigators. During the extension period, the number of subjects with serious adverse events remained at a similar level or decreased as compared to Year 1 of the study. No uterine or cervical perforations occurred during this study. No cases of pelvic inflammatory disease according to the protocol-defined criteria were diagnosed during the study.

A total of 13 subjects (6.4%) experienced at least 1 adverse event causing discontinuation of MIRENA use. Only headache was the reason for discontinuation for 2 subjects. All other adverse events causing discontinuation of MIRENA use were experienced by single subjects.

During the extension period, the numbers of subjects with adverse events causing discontinuation of MIRENA use were lower (n=3 in Year 2, n=4 in Year 3, and n=1 in Year 4) as compared to Year 1 of the study (n=5). In Year 5, no subject discontinued the use of MIRENA due to an adverse event.

No pattern of differences in blood pressure was noted over time.

Two cases of total expulsion were reported, one at 4 months and another one at 18 months after insertion of the second MIRENA. Following the first total expulsion of MIRENA, the estimated cumulative probability of total expulsion was 0.5% (at Month 6 and Year 1) and increased to 1.1% after the second total expulsion (at Month 18 through to Year 5). No partial expulsion of MIRENA occurred during this study. Thus, the estimated cumulative probability of partial expulsion was 0.0% throughout the entire study

Conclusions

- During the first year of use of the second consecutive MIRENA, bleeding profiles were even more favorable than those observed during the last 3 months of use of the first MIRENA. The removal of the first MIRENA and the insertion of the second MIRENA were considered easy by the vast majority of women and their physicians, and most women experienced no or only mild pain. The continuation rate was high, there were no pregnancies, and the women treated were extremely satisfied. The administration of sublingual misoprostol just before MIRENA insertion had no effect on insertion easiness.
- During the 5 years of use of the second consecutive MIRENA, the number of bleeding and spotting days was very low and bleeding profiles were even more favorable than those observed during the last 3 months of use of the first MIRENA.
- Investigators considered the removal of the second MIRENA as easy in the vast majority of subjects. The continuation rate was high and the subjects treated were extremely satisfied.
- One pregnancy occurred during the study: Approximately 24 months after insertion of the second MIRENA, 1 subject experienced incomplete spontaneous abortion.
- The use of the second consecutive MIRENA over 5 years was safe and well tolerated. There were no deaths during this study and none of the serious adverse events was assessed as related to MIRENA.
- Only 2 subjects experienced total expulsion of MIRENA approximately 4 months and 18 months after its insertion. No partial expulsion of MIRENA occurred during this study.

Publication(s):	Gemzell-Danielsson K, Inki P, Boubli L, O'Flynn M, Kunz M and Heikinheimo O. Bleeding pattern and safety of consecutive use of the levonorgestrel-releasing intrauterine system (LNG-IUS) - a multicentre prospective study. Hum Reprod 2010;25(2): 354-359. Heikinheimo O, Gemzell-Danielsson K. New clinical data on consecutive use of the levonorgestrel-releasing intrauterine system. Expert Rev Obstet Gynecol 2010;5(3):275–277. Heikinheimo O, Inki P, Kunz M, Parmhed S, Anttila A-M, Olsson S-E, Hurskainen R, Gemzell-Danielsson K. Double-blind, randomized, placebo-controlled study on the effect of misoprostol on ease of consecutive insertion of the levonorgestrel-releasing intrauterine system. Contraception 2010;81:481–486. Heikinheimo O, Inki P, Kunz M, and Gemzell-Danielsson K. Predictors of bleeding and user satisfaction during consecutive use of the levonorgestrel-releasing intrauterine system. Hum Reprod 2010;25(6):1423-1427.

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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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