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ORIGINAL ARTICLE ***Fertility control***

Bleeding pattern and user satisfaction in second consecutive levonorgestrel-releasing intrauterine system users: results of a prospective 5-year study

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STUDY QUESTION: What is the bleeding pattern during second consecutive levonorgestrel-releasing intrauterine system (LNG-IUS) use?

SUMMARY ANSWER: Consecutive use of LNG-IUS is associated with a predictable bleeding pattern, characterized by the absence of the initial period of irregular bleeding seen after interval insertion of an LNG-IUS and a non-bleeding pattern in the vast majority of women.

WHAT IS KNOWN ALREADY: With increased popularity of the LNG-IUS for long-term birth control and treatment of heavy menstrual bleeding (HMB), consecutive use of the system is becoming more frequent. One previous study showed 60% amenorrhea rate in consecutive IUS users; however, the sample size was small.

STUDY DESIGN, SIZE, DURATION: A prospective multicenter study in four European countries recruited women who wished to continue with LNG-IUS use immediately after the first 5-year period. A total of 204 women were followed up until the end of the first year of the second IUS. Thereafter 170 women continued into the extension phase of the study up to the full 5 years of use of the second IUS and 144 women continued to the end of the study.

PARTICIPANTS, SETTING, METHODS: A total of 170 women (mean age 39 years) who had been using their first LNG-IUS for between 4 years 3 months and 4 years 9 months, either for contraception or for treatment of HMB, and who planned to replace the device with a new LNG-IUS, were recruited and followed up to 5 years of the second IUS use. A total of 17 centers in four European countries were involved in the study. Bleeding patterns were analyzed using daily bleeding diaries using 90-day reference periods (RP) for the first year of the second IUS use and for the last RP of each year during Years 2–5 of use.

MAIN RESULTS AND THE ROLE OF CHANCE: Approximately 70% of women were free of bleeding during Years 2–5 and up to 49% were amenorrheic. There was a slight increase in the number of bleeding/spotting days of ~3 days during the first RP immediately after the placement of the second IUS, whereafter the number of bleeding/spotting days returned to the level preceding the second IUS insertion or below that. Absence of bleeding was associated with high overall satisfaction and continuation rates. No serious adverse events assessed as related to the LNG-IUS use occurred during the 5-year period. The cumulative expulsion rate during the 5-year study period was 1.2%. The sample size was large enough to study bleeding patterns, and subjects are likely to represent typical consecutive IUS users, and therefore, the role of chance is small.

LIMITATIONS, REASONS FOR CAUTION: The women represent a selected group as they had already successfully used their first IUS for almost 5 years and were willing to continue its use—however, this is currently a common clinical situation. The results may therefore not be extrapolated to first-time users of the LNG-IUS.

WIDER IMPLICATIONS OF THE FINDINGS: These data are of importance when counseling women who are making decisions concerning long-term contraception.

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Introduction

The levonorgestrel-releasing intrauterine system (LNG-IUS; initial *in vitro* release rate 20 μg LNG/24 h) has been proved a safe and very reliable method of contraception over 5 years of use. The LNG-IUS has been on the market in several European countries since the early 1990s; in the USA it was launched in 2001. Reported user satisfaction with the LNG-IUS is dependent on the level of pre-insertion counseling, with women who reported receiving a lot of advance information regarding expected bleeding pattern and adverse effects being more satisfied than less informed women (Backman *et al.*, 2002). However, large post-marketing studies have reported in general very high overall satisfaction rates ranging from 74 to 95% (Backman *et al.*, 2002, Römer and Linsberger, 2009). Long-term use of the LNG-IUS (either repeatedly—with a break between two IUSs or consecutively—continuing immediately after removal with a second IUS) is thus becoming increasingly common (Inki, 2007). While there appears to be no recent data on the proportion of repeat or consecutive users, a survey in Europe published in 2009 showed that 20% of over 8000 LNG-IUS users had previous experience with the system (Römer and Linsberger, 2009). The overall satisfaction among these women was 99% (Römer and Linsberger, 2009). In the treatment of heavy menstrual bleeding (HMB), a study from Spain reported that 88% of LNG-IUS users who continued to 5 years with the first system and had not reached menopause at that time, elected to have a new system placed (Lete *et al.*, 2011), showing the high acceptability of the system also in the treatment of HMB.

So far, few studies have specifically studied the population of consecutive IUS users. One prospective study from Sweden reported on the bleeding patterns in 82 women who chose to have the second LNG-IUS inserted after completion of the first part of a large European multicenter study (Rönnerdag and Odlind, 1999). In that study 70% of women had regular scanty bleeding, 4% had infrequent bleeding and 26% were in amenorrhea during the first 5-year period of the LNG-IUS use. However, during the second 5-year segment of the LNG-IUS use, only ~30% of women had regular scanty bleeding, 10% had infrequent bleeding and ~60% were in amenorrhea. Importantly, the initial spotting frequently observed after insertion of the first LNG-IUS did not recur after placement of the second LNG-IUS. In addition, there was only one partial expulsion during the use of the second consecutive LNG-IUS, suggesting that the expulsion rate could be lower than that observed after the first LNG-IUS insertion. Another prospective study from Brazil reported no difference in the bone mineral density among women who had used the IUS consecutively up to 10 years, when compared with copper intrauterine device users (Bahamondes *et al.*, 2010). Recently, the 10-year follow-up results of an RCT of LNG-IUS versus hysterectomy for HMB were published (Heliövaara-Peippo *et al.*, 2013). During 10 years, a total of 55 women out of the 119 randomized to LNG-IUS (46%) had undergone hysterectomy; however, only 5 of the hysterectomies took place during the second IUS use (Years 5–10). The health-related quality of life and psychosocial well-being was similar between the groups of IUS users and women randomized to hysterectomy, while the costs remained 31% lower in the IUS group even after 10 years.

The present study aimed to evaluate the bleeding profile, the removal and insertion procedures, the menstrual comfort and overall satisfaction, and the reasons leading to premature removal of the LNG-IUS in women who had their first LNG-IUS replaced with a second LNG-IUS at the same visit. Previously, we have published the results of the bleeding pattern analysis over the first year of the second consecutive LNG-IUS use (Gemzell-Danielsson *et al.*, 2010, Heikinheimo *et al.*, 2010a,b). In addition, we have analyzed which factors could influence the bleeding pattern during the second consecutive LNG-IUS, and found that, for example, indication of use (contraception versus HMB) did not have an effect on the bleeding pattern (Heikinheimo *et al.*, 2010a,b). During the original study, it was decided to amend the study protocol to include the follow-up during Years 2–5 of the second consecutive LNG-IUS. This report presents the results of this extension part of the study with regard to continuation rates, user satisfaction, bleeding patterns, efficacy and safety.

Materials and Methods

Study design, subjects and efficacy measures

The study design has been previously described (Gemzell-Danielsson *et al.*, 2010). In brief, this was a prospective multicenter study, performed at 17 clinics in Finland, France, Ireland and Sweden. Women of reproductive age who had been using their first LNG-IUS (Mirena®, Bayer Oy, Turku, Finland) for between 4 years 3 months and 4 years 9 months, either for contraception or for treatment of HMB, and who planned to replace the device with a new LNG-IUS, were recruited. The inclusion and exclusion criteria have been previously described (Gemzell-Danielsson *et al.*, 2010). To exclude the possibility that menopausal status could influence the bleeding pattern (which was the primary efficacy parameter, see below), menopausal symptoms impairing the subject's quality of life or current estrogen therapy for menopausal symptoms were exclusion criteria.

The subjects attended a follow-up visit once yearly throughout Years 2–5 and underwent the following assessments/procedures at each visit: palpation of breasts, pelvic examination, blood pressure measurement, recording of adverse events (AEs) and concomitant medications, and collection of the menstrual comfort and satisfaction questionnaire. In the questionnaire, subjects were asked about their level of agreement regarding statements on satisfaction with bleeding or absence of bleeding, bleeding pattern, menstrual

pain, premenstrual symptoms and overall satisfaction. In addition, every second year (Years 3 and 5) a PAP smear and gynaecological ultrasound examination were performed. Ovarian cysts without any symptoms were only to be reported as AEs if they were abnormal non-functional cysts and/or had a diameter >30 mm.

The primary efficacy variable of the study was the bleeding pattern, measured using daily bleeding diaries filled out by the participants with 90-day reference periods (RP) for the last 3 months of the first LNG-IUS, during the first year of the second LNG-IUS (reported previously Gemzell-Danielsson *et al.*, 2010) and during one RP in each of the Years 2–5. For each RP, the following parameters were displayed: number of bleeding/spotting days; number of bleeding days (excluding spotting days); number of spotting-only days; number of subjects with no bleeding and no spotting (amenorrhea) and number of subjects with no bleeding (spotting allowed).

Annual continuation rates were evaluated annually using a Kaplan–Meier estimates. The Pearl Index was calculated for the overall treatment period of 5 years for subjects who had not had sterilization. Pearl Indexes were calculated separately for subjects who were ≤40 years of age at insertion of the second LNG-IUS and for those subjects who were >40 years at insertion of the second LNG-IUS. The scores of menstrual comfort and overall satisfaction were analyzed descriptively. AEs were coded using an internationally recognized dictionary (MedDRA) and analyzed descriptively. Blood pressure, gynaecological examination and breast palpation findings were presented in terms of descriptive statistics.

Statistical methods

All variables were analyzed by descriptive statistical methods. The number of data available, mean, SD, minimum, quartiles, median and maximum were calculated for metric data. Frequency tables were generated for categorical data. Dropout rates were provided by year using a Kaplan–Meier analysis of time until dropout.

All analyses were performed on the full analysis set (FAS). The FAS included subjects who received the second consecutive LNG-IUS (including one woman with unsuccessful insertion attempt). The FAS was the relevant set for safety analyses. AEs were reported according to MedDRA Version 15.1. Efficacy and demographics are presented for the subjects that continued in the extension phase of the study (Years 2–5 of the second IUS).

Ethical approval

The protocol and all protocol amendments were submitted to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) for review. Protocol amendments implying substantial changes were approved by the appropriate IEC/IRB prior to implementation. Written informed consent was obtained from all women participating in the extension phase of the study. The study was web-posted at www.clinicaltrials.gov (trial number NCT00393198).

Results

Study flow and continuation rates

The study flow chart is presented in Fig. 1. Originally, the study recruited 204 subjects out of 234 eligible. Out of the 204, a total of 170 subjects agreed to participate in the extension period (Years 2–5 of the second LNG-IUS use). The reason for the drop in the number of participants was that the study was initially planned as a 1-year study only, and the study centers in Ireland chose not to participate in the extension phase. Out of the total of 170 subjects, altogether 26 subjects (15.3%) discontinued the LNG-IUS use prematurely during the extension

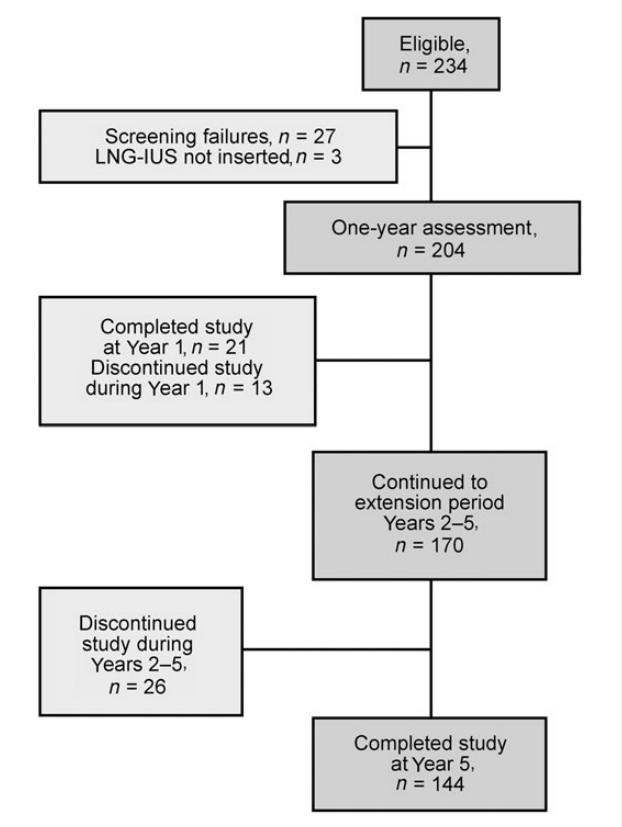

Figure 1 Study flow chart for a study of second consecutive use of the levonorgestrel-releasing intrauterine system (LNG-IUS).

Table 1 Baseline and demographic characteristics of women using a second consecutive levonorgestrel-releasing intrauterine system (LNG-IUS) who continued for up to 5 years in the extension phase of the study.

Characteristic	Total, *n* = 170 (100%)
Age (years) (mean ± SD)	38.7 ± 4.5
Age group	
≤30 years	7 (4.1)
>30 to ≤40 years	94 (55.3)
>40 years	69 (40.6)
Baseline BMI (kg/m^2) (mean ± SD)	24.31 ± 3.56
Parity	
Nulliparous	6 (3.5)
Parous	164 (96.5)
Current smoker	
Yes	32 (18.8)
No	138 (81.2)

The data are reported as *n* (%) unless stated otherwise.

period, while 144 subjects (84.7%) completed the extension period at Year 5. The baseline and demographic characteristics of the study population are shown in Table I.

Out of the 26 subjects who discontinued the study, a total of 19 subjects (11.2% of the total population) discontinued due to reasons unrelated to AEs (Table II). Subjects lost to follow-up ($n = 6$) were reported as discontinuations. Altogether 7 subjects (4.1% of the total population) discontinued due to reasons related to AEs (Table II). Two of these discontinued due to hormonal AEs (depressed mood and headache in one case and alopecia in one case).

The Kaplan–Meier estimate for continuation with the LNG-IUS during Years 2–5 is shown in Fig. 2.

Table II Reasons for discontinuation of the second consecutive LNG-IUS during Years 2–5.

Reason	*n* (%)
Reasons unrelated to AEs	19 (11.2)
Lost to follow-up	6
Missing information	3
Withdrawal of consent	3
Pregnancy	1
Other (e.g. wish for pregnancy)	6
Reasons related to AEs	7 (4.1)
Abdominal/pelvic pain	2
Expulsion	1
Hormonal	2
Intrahepatic lipoma	1
Climacteric symptoms	1

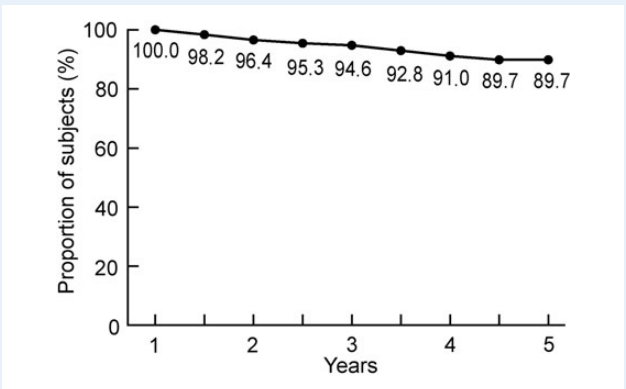

Figure 2 Kaplan–Meier estimate for continuation with the LNG-IUS during Years 2–5.

Bleeding patterns

The number of bleeding/spotting days was determined by 90-day RP. Compared with the first year of use of the second LNG-IUS this remained at a very low and constant level during Years 2–5 of the second consecutive LNG-IUS (Table III). When analyzed during the last 90-day RP of each year the mean number of bleeding/spotting days per 90-day RP was ~6 and median was 1–2 days (Table III). The median number of bleeding days was 0 at all observation points. The median number of spotting days was 2 at the end of the first year of use and 0–1 thereafter (data not shown).

During the use of the second LNG-IUS, the proportion of women without bleeding (spotting allowed) increased after the first year and remained at ~72% during Years 2–5 (Fig. 3). Similarly, the proportion of women without any bleeding and spotting (amenorrheic women) increased after the first year and remained at 44–49% during Years 2–5 (Fig. 3).

Overall satisfaction

The overall satisfaction was recorded at each visit by asking the subjects' level of agreement with the statement 'I am satisfied with the LNG-IUS'. At each visit during Years 1–5 of the consecutive LNG-IUS, over 95% of subjects definitely agreed or somewhat agreed with this statement (data not shown). The level of overall satisfaction at the last visit or at premature discontinuation is shown in Fig. 4. The results of the satisfaction with menstrual pattern were also high, ranging from 88 to 94% at various time points (data not shown). For subjects reporting amenorrhea, satisfaction rate was 100%, except for Year 2 where one subject stated dissatisfaction with amenorrhea (this subject did not discontinue the use of the IUS, however). At the last visit at Year 5 or at premature discontinuation, the subjects were asked if they intended to continue with the LNG-IUS, and 79% definitely agreed (Fig. 4).

Pregnancy rate and AEs

One subject experienced an incomplete spontaneous abortion at ~2 years after the placement of the second LNG-IUS. There were no other pregnancies. The Pearl Index was 0.21 (95% CI 0.01–1.14)

Table III Number of bleeding/spotting days by 90-day reference period during the second consecutive LNG-IUS use.

Time (years)	*n*[a]	Mean	SD	Median	25% percentile	75% percentile
1	159	6.0	7.3	4.0	0.0	10.0
2	154	5.8	8.6	2.0	0.0	8.0
3	143	5.5	8.1	1.0	0.0	9.0
4	135	5.1	7.7	2.0	0.0	8.0
5	135	5.8	7.9	2.0	0.0	9.0

Bleeding and spotting were reported during the last 90-day reference period of each year of use.
[a]Number of bleeding diaries fulfilling the validity criteria.

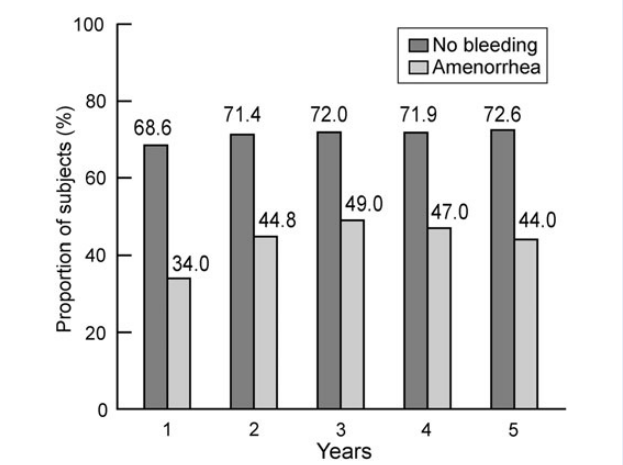

Figure 3 Proportion of subjects (%) with no bleeding (but with ≥1 day of spotting during a 90-day reference period) and with amenorrhea (no bleeding or spotting days during a 90-day reference period) during second consecutive LNG-IUS. The bleeding data were collected by means of daily bleeding diaries. The result of the last 90-day reference period during each year is shown.

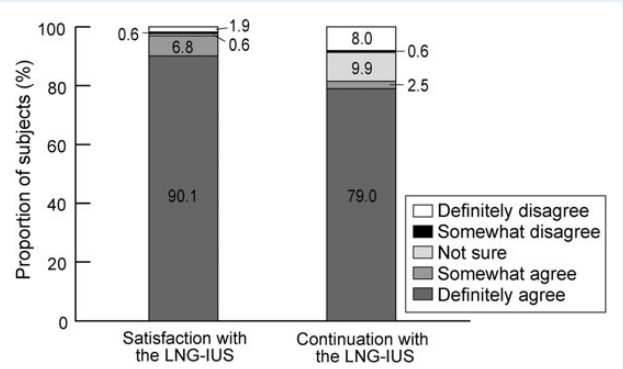

Figure 4 Overall satisfaction and continuation with the second consecutive LNG-IUS at 5 years or at premature termination of the study. The women were asked to rate their level of agreement using a 5-degree Likert-like scale on the following statements: 'I am satisfied with the LNG-IUS' and 'I will continue with the LNG-IUS'. Proportion of subjects (%) stating different levels of agreement is shown.

among subjects aged ≤40 years (486.7 woman years) and 0.0 (95% CI 0.00–1.09) among subjects aged >40 years (337.8 woman years).

During the entire 5-year study period, 167 of 204 subjects of the FAS (81.9%) experienced at least one treatment-emergent AE (regardless of association with the LNG-IUS). Only 36 subjects (17.6%) experienced at least one AE considered related to the LNG-IUS as assessed by the investigator. The treatment-emergent AEs occurring in ≥5% of subjects are summarized in Table IV for the 5-year study period. Among these, most common were ovarian cyst (10.3%), cervical dysplasia (9.8%), headache (9.8%) and vaginal infection (9.8%). Out of the 21 subjects diagnosed with ovarian cyst, none discontinued the use of the LNG-IUS due to this AE, and none required any surgery.

Table IV Number of subjects with common (≥5%) treatment-emergent AEs (according to MedDRA terminology by preferred term; full analysis set, *n* = 204).

AEs which occurred in ≥5% of the subjects	*n*	%
Ovarian cyst	21	10.3
Cervical dysplasia[a]	20	9.8
Headache	20	9.8
Vaginal infection	20	9.8
Sinusitis	18	8.8
Acne	16	7.8
Influenza	14	6.9
Back pain	13	6.4
Candidiasis	13	6.4
Abdominal pain	12	5.9
Breast pain	12	5.9
Urinary tract infection	12	5.9
Fungal infection	11	5.4

[a]Does not refer to histologically confirmed dysplasia but mostly 'abnormal squamous cells of undetermined significance', coded under preferred term 'cervical dysplasia' by MedDRA terminology.

Out of the 20 subjects (9.8%) with an AE coded by the MedDRA preferred term 'cervical dysplasia', 17 (8.3%) were diagnosed with 'ASC-US' or 'atypical squamous cells of undetermined significance', 3 (1.5%) with 'LSIL' ('LSIL' refers to 'low-grade squamous intraepithelial lesion', one subject had both ASC-US and LSIL) and 1 (0.5%) with 'cervical dysplasia'. It should be noted that according to MedDRA, all of these low-level terms are summarized under the preferred term 'cervical dysplasia. However, the majority of the low-level terms did not indicate histologically confirmed cervical dysplasia. None of the 20 subjects with the MedDRA preferred term 'cervical dysplasia' discontinued use of the LNG-IUS due to this AE. One subject underwent a colposcopy and one subject a laser treatment of the cervix (both without removal of the LNG-IUS), while no other cervical procedures were performed for the other 18 women.

During 5 years, no cases of uterine or cervical perforation, pelvic inflammatory disease or partial expulsion occurred. Two complete expulsions occurred (at 6 and 18 months after insertion of the second LNG-IUS), thus the cumulative expulsion rate was 1.2% at 5 years.

There were no deaths during this study. A total of 16 subjects experienced treatment-emergent serious AEs. None of those events was assessed as related to the LNG-IUS by the investigators.

Laboratory tests and examinations

Overall, there were no notable changes in systolic or diastolic blood pressure throughout the entire 5-year study period (data not shown). Gynaecological ultrasound examinations and PAP smears were classified as safety parameters, and these were performed at Years 3 and 5 (with a 5-year rate containing all subjects who continued to full 5 years or who had prematurely discontinued the study). Altogether 154 and 161 subjects had the ultrasound examination performed at 3 and 5 years, respectively. There were no abnormal endometrial findings at these examinations. A total of 12 subjects (7.8%) and 16 subjects (9.9%) had at least one fibroid demonstrable at the examination, ranging from 4 to

69 mm in diameter (data not shown). A total of 16.2 ($n = 25$) and 12.6% ($n = 20$) had an ovarian cyst demonstrable at 3 and 5 years/premature discontinuation, respectively, ranging from 5 to 49 mm in cross-sectional diameter. Altogether 150 and 148 subjects had the PAP smear taken at 3 and 5 years, respectively, and the cervical smears were abnormal in 5.3 ($n = 8$) and 8.1% ($n = 12$) at these time points, respectively. A total of five subjects reported increased weight (2.5%) and one subject decreased weight (0.5%) during the study, with no subject discontinuing due to either reason.

Discussion

We found that during consecutive use of a second LNG-IUS, bleeding patterns remain predictable with increasing rates of amenorrhea during Years 2–5. Efficacy, overall satisfaction and continuation rates are maintained at high levels, while the rates of AEs resulting in termination of the LNG-IUS use are low. Compared with the bleeding patterns observed during the first year of use of a second consecutive LNG-IUS, fewer women reported any bleeding and more women developed amenorrhea during the extension phase of the study.

The present study analyzed systematically bleeding pattern and satisfaction and safety during long-term use of the LNG-IUS, using daily bleeding diaries. It must be kept in mind that the women who participated were highly selected—they had already used the IUS for almost 5 years and were willing to continue its use. This represents currently a common clinical situation, as many women consecutively use the LNG-IUS for both contraception and treatment of HMB (Inki 2007; Lete *et al.*, 2011). Accordingly, the user satisfaction and continuation rates were high in the present study, with almost 90% of women continuing from 2 to up to 5 years with the second IUS. The selected nature of the study subjects is also reflected by the fact that nearly all of them had complete follow-up.

The analysis of the bleeding diaries showed very little bleeding/spotting during the study—~70% of women were free of bleeding during Years 2–5 and 34–49% were amenorrheic. There was a slight increase in the number of bleeding/spotting days of ~3 days during the first 90-day RP immediately after the placement of the second IUS, thereafter the number of bleeding/spotting days remained at baseline or below baseline. A previous small study reported on the bleeding patterns during consecutive use of an LNG-IUS in 82 women (Rönnerdag and Odlind, 1999). The study showed 60% amenorrhea rate during Years 7–12 of consecutive LNG-IUS use—; however, during the study 8.5% of subjects became post-menopausal which could explain the higher amenorrhea rate observed in that study. In the present study, women were to be excluded from the study in case they developed climacteric symptoms and started estrogen therapy to exclude the possibility of menopausal status affecting the bleeding patterns (however only one subject discontinued the study for this reason).

The high rate of amenorrhea/absence of bleeding was well accepted by the participants, as shown by the high proportion of subjects reporting satisfaction with their bleeding pattern. Amenorrhea in particular was associated with high user satisfaction of 100% at all time points, with the exception of one subject not being satisfied with amenorrhea at 2 years of use. Satisfaction with the non-bleeding pattern is also shown by the fact that no subject discontinued the use of the IUS during Years 2–5 because of either bleeding problems or amenorrhea.

AEs were consistent with those seen among this age group of women, and <20% of women experienced AEs considered related to the LNG-IUS. The most common treatment-emergent AEs were ovarian cysts. According to the study protocol, these were to be reported as AEs if they were abnormal non-functional cysts and/or had a diameter >30 mm. However, none of the subjects with ovarian cysts required surgical intervention and most were asymptomatic. Moreover, only two women underwent further diagnostic or therapeutic interventions as a result of an abnormal PAP smear.

Among the few discontinuations, the majority were not related to AEs. The most common reason for discontinuation was loss to follow-up or miscellaneous personal reasons, e.g. wish for pregnancy. Only 4% of the study subjects terminated the use of the LNG-IUS due to AEs, which were mostly hormonal in nature. The cumulative expulsion rate during the whole 5-year period was 1.2%. The rate of discontinuations reported earlier by Rönnerdag and Odlind (1999) was 11%, and also in this study the most common reason was loss to follow-up. Similarly, the expulsion rate was low with one partial expulsion occurring among the 82 subjects (1.2%). Thus, the results of these two studies are consistent, and show a very low rate of discontinuations due to treatment-emergent AEs. Expulsion rates in first-time LNG-IUS users have been up to 6% at 5 years (Andersson *et al.*, 1994), thus it appears that the rate of expulsion in consecutive use is lower.

We conclude that the 5-year continuation rate of the second LNG-IUS among women who choose to continue its use is remarkably high. Consecutive use of the LNG-IUS is associated with a predictable bleeding pattern, characterized by a non-bleeding pattern in the vast majority of women, which was well accepted, as shown by the high satisfaction rate regarding bleeding pattern and amenorrhea in particular. The expulsion rate is lower during consecutive use of the IUS, when compared with first-time use. These data are of importance when counseling women who are making decisions concerning long-term contraception.

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Authors' roles

All authors were involved in the study concept design. P.I. and T.S. acquired the clinical data, which was interpreted by all authors. P.I. drafted the manuscript, which was critically revised by all other authors for intellectual content. All authors approved the final version of the manuscript for publication.

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Conflict of interest

P.I. and T.S. are full-time employees of Bayer Pharma AG. O.H. and K. G-D. have received consultancy fees from Bayer Pharma AG. The publication was developed jointly by all authors without third-party involvement and no honoraria were paid for any authors for their contribution to this manuscript.

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