A 12-month multicenter, randomized study comparing the levonorgestrel intrauterine system with the etonogestrel subdermal implant

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Objective: To compare the levonorgestrel intrauterine system (LNG-IUS 8), which has an average levonorgestrel release rate of ~8 μg/24 hours during the first year (total levonorgestrel content 13.5 mg; Jaydess/Skyla), with the etonogestrel (ENG) subdermal implant (total content, 68 mg) with regard to the 12-month discontinuation rate (primary outcome).
Design: Randomized, open-label, phase III study.
Setting: Thirty-eight centers in six European countries.
Patient(s): Study population of 766 healthy nulliparous and parous women aged 18–35 years.
Intervention(s): The LNG-IUS 8 or the ENG implant.
Main Outcome Measure(s): Discontinuation rate, by treatment group, at Month 12.
Result(s): The 12-month discontinuation rates were 19.6% and 26.8% in the LNG-IUS 8 and ENG implant groups, respectively. The −7.2% difference was statistically significant (95% confidence interval −13.2%, −1.2%). Fewer women in the LNG-IUS 8 group than in the ENG implant group discontinued because of increased bleeding (3.2% vs. 11.3%) or adverse events (14.3% vs. 21.8%). At 12 months, more women in the LNG-IUS 8 group than in the ENG implant group were "very/somewhat satisfied" with their bleeding pattern (60.9% vs. 33.6%) and reported a preference to use their study treatment after study completion (70.1% vs. 58.5%).
Conclusion(s): The LNG-IUS 8 was associated with a significantly lower 12-month discontinuation rate compared with the ENG implant; mainly because ENG implant users frequently discontinued due to increased bleeding. More LNG-IUS 8 users than ENG implant users reported being "very/somewhat satisfied" with their bleeding pattern, and reported a preference to continue using their study treatment after the study.
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Key Words: LNG-IUS, etonogestrel implant, contraception, discontinuation, LARC

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The high global incidence of unintended pregnancy (1) could be addressed through more widespread use of highly effective long-acting reversible contraception (LARC) methods (2), which are suitable for a wide range of women regardless of age or parity (3). Through provision of counseling on LARC methods, as well as appropriate access to these methods, unintended pregnancy rates (PRs) could be reduced (4, 5).

A smaller, lower-dose LARC method is available: the levonorgestrel

intrauterine system (LNG-IUS). Its total content is 13.5 mg (average, ~8 μg/24 hours during the first year; LNG-IUS 8; Jaydess/Skyla, Bayer Pharma AG) (6). This device is placed with a narrower insertion tube than the LNG-IUS with total content of 52 mg (average, ~20 μg/24 hours during the first year; LNG-IUS 20; Mirena, Bayer Pharma AG) (3.80 mm (7) vs. 4.40 mm (8), respectively) and may appeal to a wider range of women. In a pivotal phase III study, LNG-IUS 8 was highly effective in both nulliparous and parous women, in younger (≤25 years) and older (26–35 years) women, and was associated with a favorable safety profile (7).

The etonogestrel (ENG) subdermal implant (total content, 68 mg; Nexplanon, Merck Sharp & Dohme) (9), which is bioequivalent to the previous ENG subdermal implant (total content, 68 mg; Implanon, Merck Sharp & Dohme) (10), is preloaded into a novel applicator to facilitate insertion (10). The ENG implant is a highly effective contraceptive method with a favorable 3-year safety profile in women aged 18–40 years (9).

This phase III trial was conducted to compare the use of LNG-IUS 8 with the ENG implant in nulliparous and parous women.

MATERIALS AND METHODS

Study Design

This multicenter, randomized, open-label study (ClinicalTrials.gov: NCT01397097) was conducted between September 2011 and June 2013 at 38 centers in Australia, Finland, France, Norway, Sweden, and the United Kingdom. The protocol and its amendment were reviewed and approved by each study site's Independent Ethics Committee or Institutional Review Board. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. Written informed consent was obtained from all subjects before study entry.

Inclusion and Exclusion Criteria

Healthy nulliparous and parous women aged 18–35 years (inclusive) requesting contraception were recruited. Women were required to have a normal or clinically insignificant cervical smear (i.e., not requiring further follow-up) within 6 months before screening and to have regular menstrual cycles (21–35 days). Women were excluded if they had had a vaginal delivery, cesarean section, or abortion within 6 weeks before screening. For further exclusion criteria, see Supplemental Material (available online).

Treatment Groups and Randomization

Treatment allocation was performed with a computer-generated randomization list provided by the sponsor's randomization management. Each randomization number was assigned to either the LNG-IUS 8 or the ENG implant and randomization numbers were distributed in sets in a 1:1 format to each group. Randomization envelopes were prepared for each study site, consisting of complete randomization sets. Eligible women were assigned to envelopes in ascending order to ensure the randomization as planned.

After 12 months, women had the option to continue using their study treatment for an additional 2 years (total, 3 years). However, only women using LNG-IUS 8 were followed beyond 12 months. The data reported here are from the 12-month randomized study only.

Study Treatment

The LNG-IUS 8 and the ENG implant were evaluated. Up to two placement attempts were permitted per woman; if both attempts failed, the woman was withdrawn from the study. Use of local anesthesia or oral analgesics was permitted at the investigators' discretion. Women were allowed to use barrier methods for protection against sexually transmitted infections and were required to record this form of back-up contraception.

Study Visits and Evaluations

Scheduled study visits took place at screening, randomization (for LNG-IUS 8 placement or ENG implant insertion), and Months 1, 6, and 12 (end of study [EOS]). Pregnancy tests were performed at screening, randomization, and Month 12/EOS. For premature discontinuations, all examinations were to be performed within ±4 weeks of the premature discontinuation date. During this visit, reasons for premature discontinuation were assessed by the investigator using a case report form. Investigators cited the reason "lost to follow-up" only in cases when there was no possibility of contacting the woman anymore. Overall satisfaction with study treatment was assessed at Months 6 and 12/EOS by the subject and entered into a case report form by the investigator. User satisfaction with study treatment was assessed by subjects using a five-point Likert item questionnaire, with the options of "very satisfied," "satisfied," "neither satisfied nor dissatisfied," "dissatisfied," and "very dissatisfied." The questionnaire was completed by subjects at Months 6 and 12/EOS in a quiet, private environment. Overall satisfaction rate was defined as the percentage of women in each treatment group reporting they were "very satisfied" or "satisfied" with treatment. Women recorded daily bleeding in diaries as "none," "spotting" (need for panty liners only), "light" (need for sanitary protection but less than normal menstruation), "normal" (relative to the woman's own experience), or "heavy" (more than normal menstruation in the woman's own experience). Adverse events, including those of special interest (pelvic inflammatory disease, uterine perforation, ectopic pregnancy [EP], expulsion, and ovarian cysts [>3 cm in diameter on ultrasound or abnormal, nonfunctional cysts]), were also recorded. Vaginal ultrasound examinations were not routinely scheduled but may have been performed by the investigator if thought to be necessary to evaluate symptoms of ovarian cyst or other pelvic pathology.

Study Outcomes

The primary outcome was discontinuation rate, by treatment group, at Month 12. Secondary outcomes included discontinuations by reason at Month 12, Pearl index (PI), overall user satisfaction, user satisfaction and bleeding questionnaire

results, bleeding profile, and safety profile in the LNG-IUS 8 and ENG implant groups.

Statistical Analyses and Determination of Sample Size

Based on data from previous studies, 12-month discontinuation rates of approximately 14% for LNG-IUS 8 (7, 11) and 19.8% for the ENG implant (12) were assumed. A sample size of 760 women was determined to provide 90% power to demonstrate noninferiority for LNG-IUS 8 compared with the ENG implant in discontinuation rates (primary objective; with a 3% noninferiority margin) at a one-sided α-level of 2.5%. The overall 12-month discontinuation rate in each treatment group was determined using Kaplan-Meier analysis. The 12-month discontinuation rates were compared for noninferiority and superiority of LNG-IUS 8 versus the ENG implant. These tests were performed by comparing the upper limit of the 95% confidence interval (CI) for the difference in proportions (i.e., the 12-month discontinuation rate of LNG-IUS 8 minus the 12-month discontinuation rate of the ENG implant) with 3% (the noninferiority margin) and 0 (the superiority margin). For noninferiority, the upper limit of the 95% CI for the difference in proportions had to be >3%. For superiority, the upper limit of the 95% CI for the difference in proportions had to be >0. Superiority testing was only performed if noninferiority could be established. Twelve-month discontinuation rates, by reason for discontinuation, were also assessed. Women in each treatment group selected a reason for discontinuation from a predetermined list. The PR was expressed as the PI (number of pregnancies per 100 woman-years); 95% CI calculations assumed that the number of pregnancies followed a Poisson distribution. The cumulative failure rate was calculated for each treatment group using Kaplan-Meier analysis. Times during which women used concomitant contraception were subtracted from exposure times used for the calculations.

Overall user satisfaction with study treatment was analyzed by the last observation carried forward method, which accounted for women who prematurely discontinued. Satisfaction ratings reported at premature discontinuation were assigned to the closest missing visit (for Months 6 and 12) and subsequently carried forward. Bleeding patterns during 12 months were evaluated using 90-day and 28-day reference intervals (RIs). The modified intention-to-treat set comprised all women for whom at least one placement attempt with LNG-IUS 8 or insertion attempt with the ENG implant was made. The full analysis set comprised all women for whom an LNG-IUS 8 or ENG implant was successfully placed or inserted.

RESULTS

Study Subjects

Of 952 subjects screened for inclusion, 766 were randomized; 385 to LNG-IUS 8 and 381 to the ENG implant (Supplemental Fig. 1, available online). The LNG-IUS 8 placement was attempted in 382 of 385 women (modified intention-to-treat) and was successful at the first attempt in 375 women (98.2%). Four women had a second placement attempt, which was successful in three women (378/385 women [98.2%] in total) (full analysis set). The ENG implant insertion was successful in all 381 women. Therefore, all were included in the full analysis set and modified intention-to-treat. Local anesthesia was administered to 14.9% of LNG-IUS 8 users and 99.5% of ENG implant users. However, data were missing for 160 LNG-IUS 8 users and two ENG implant users. Baseline characteristics are summarized in Table 1.

Study Discontinuations

The 12-month discontinuation rates in the LNG-IUS 8 and ENG implant groups were 19.6% and 26.8%, respectively, and noninferiority was demonstrated. The upper 95% CI of −1.2% for the difference in proportions was <3% (the noninferiority margin; $P=.0004$) (Table 2). In additional superiority analyses, the 12-month discontinuation rate was significantly lower with LNG-IUS 8 than with the ENG implant. The upper 95% CI for the difference in proportions was <0% ($P=.0092$) (Table 2). The most common reason for discontinuation at Month 12 was bleeding pattern alteration, mainly attributable to "increased bleeding" (11.3% in the ENG implant group, 3.2% in the LNG-IUS 8 group; Table 2).

Contraceptive Efficacy

Three pregnancies (one intrauterine [IUP], one EP, and one biochemical [transient serum β-hCG increase]) were reported—all within the LNG-IUS 8 group. In all three cases the LNG-IUS 8 was still in situ, and estimated conception dates were 88, 310, and 349 days after LNG-IUS 8 placement.

TABLE 1

Baseline characteristics (modified intention-to-treat set[a]).

Variable	LNG-IUS 8 (n = 382)	ENG implant (n = 381)
Mean age, y (range)	24.8 (18–35)	25.0 (18–35)
Mean BMI, kg/m^2 (range)	23.6 (15.3–46.0)	24.3 (16.4–44.0)
Nulliparous, n (%)	291 (76.2)	275 (72.2)
Mean duration of menses (d)	5.0	5.0
Mean cycle length (d)	28.5	28.7
Mean uterine depth (cm)	7.2	Not relevant
Contraceptive method used at screening, n (%)		
Oral hormonal contraception	169 (44.2)	175 (45.9)
Barrier methods	131 (34.3)	127 (33.3)
Vaginal hormonal contraception	27 (7.1)	23 (6.0)
LNG-IUS	11 (2.9)	10 (2.6)
Implants	6 (1.6)	11 (2.9)
Transdermal hormonal contraception	5 (1.3)	7 (1.8)
IUD	5 (1.3)	4 (1.0)
Other	0	1 (0.3)
None	28 (7.3)	23 (6.0)

Note: BMI = body mass index; ENG = etonogestrel; IUD = intrauterine device; LNG-IUS 8 = levonorgestrel intrauterine system total content 13.5 mg (average, ~8 μg/24 hours during the first year).

[a] Modified intention-to-treat set: all women for whom at least one placement/insertion attempt was made.

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TABLE 2

Discontinuations at 12 months and by selected reasons of interest (full analysis set[a]).

Reason for discontinuation	LNG-IUS 8 (n = 378)	ENG implant (n = 381)
Premature discontinuation (any reason), n (%)	74 (19.6)	102 (26.8)
Difference in the proportions	−7.2%[b] (95% CI −13.2%, −1.2%)	
Non-AE-related reason, n (%)	20 (5.3)	19 (5.0)
Wish for pregnancy	3 (0.8)	4 (1.0)
AE-related reason, n (%)	54 (14.3)	83 (21.8)
LNG-IUS 8 expulsion	3 (0.8)	Not relevant
ENG implant site infection or expulsion	Not relevant	0
Bleeding pattern alterations	16 (4.2)	44 (11.5)
Increased bleeding[c]	12 (3.2)	43 (11.3)
Decreased bleeding[c]	1 (0.3)	0
Unspecified or irregular bleeding[c]	3 (0.8)	1 (0.3)

Note: AE = adverse event; CI = confidence interval; ENG = etonogestrel; LNG-IUS 8 = levonorgestrel intrauterine system total content 13.5 mg (average, ~8 μg/24 hours during the first year); MedDRA = Medical Dictionary for Regulatory Activities.
[a] Full analysis set: all women who had a successful placement/insertion.
[b] $P = .0004$ for noninferiority; $P = .0092$ for superiority.
[c] MedDRA preferred term.

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The IUP resulted in elective abortion, and the EP was medically managed. The PIs for LNG-IUS 8 and the ENG implant were 0.9 (95% CI 0.2, 2.6) and 0.0 (95% CI 0.0, 1.2), respectively. The relevant exposure duration was 333.6 woman-years in the LNG-IUS 8 group and 312.7 woman-years in the ENG implant group. Kaplan-Meier estimates for the 12-month cumulative failure rates when using LNG-IUS 8 and the ENG implant were 1.0% and 0, respectively.

Overall User Satisfaction

At all time points (Months 6, 12, and 12/EOS), overall treatment satisfaction was significantly higher with LNG-IUS 8 than with the ENG implant (95% CIs for the two treatments do not overlap at any time point; Table 3). At Month 12, among the 327 and 319 women in the LNG-IUS 8 and ENG implant groups, respectively, who completed the overall satisfaction questionnaire, 53.8% and 49.5% were "very satisfied," 32.7% and 26.3% were "satisfied," 6.7% and 10.3% were "neither satisfied nor dissatisfied," 5.8% and 11.9% were "dissatisfied," and 0.9% and 1.9% were "very dissatisfied," respectively.

TABLE 3

Overall satisfaction with study treatment (last observation carried forward analysis; full analysis set[a]).

	LNG-IUS 8		ENG implant	
Visit[b]	n	Satisfaction rate, % (95% CI)[c]	n	Satisfaction rate, % (95% CI)[c]
Month 6	365	82.7 (78.5, 86.5)	369	71.3 (66.4, 75.8)
Month 12	327	86.5 (82.4, 90.1)	319	75.9 (70.8, 80.5)
Month 12/EOS	369	80.2 (75.8, 84.2)	372	66.1 (61.1, 70.9)

Note: CI = confidence interval; ENG = etonogestrel; EOS = end of study; LNG-IUS 8 = levonorgestrel intrauterine system total content 13.5 mg (average, ~8 μg/24 hours during the first year).
[a] Full analysis set: all women who had a successful placement/insertion.
[b] For women who discontinued prematurely, assessments of the premature discontinuation visit were assigned to the closest missing visit for Months 6 and 12. For Month 12/EOS, assessments were carried forward from the previous visit.
[c] Satisfaction rate: combined percentages of women reporting that they were "satisfied" or "very satisfied" in response to the following question "How satisfied are you with the birth control method used during the study?"

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Further User Satisfaction and Bleeding Questionnaire Outcomes

At 12 months, in response to the question "If given a choice, after completion of the study, you would: continue with the study treatment; use a different hormonal contraceptive; use a different contraceptive method; discontinue use of all types of contraceptives; no need for contraceptive at this time; don't know," 70.1% of LNG-IUS 8 users and 58.5% of ENG implant users stated that they would continue their study treatment beyond study completion, and 2.2% of LNG-IUS 8 users and 3.3% of ENG implant users stated they had no need for contraception at that time. In response to the question "Since your last study visit, when you had menstrual bleeding, how satisfied were you with your menstrual bleeding pattern?," at 12 months, 60.9% of LNG-IUS 8 users were "very satisfied" or "somewhat satisfied" with their bleeding pattern compared with 33.6% of ENG implant users. Among women who were amenorrheic, in response to the question "How satisfied were you with the absence of menstrual bleeding?," 78.7% of LNG-IUS 8 users and 77.7% of ENG implant users reported being "very satisfied" with bleeding absence at Month 12.

Bleeding Profiles

In both treatment groups, the mean and median number of bleeding days decreased over time during use (Supplemental Fig. 2, available online). The mean number of combined bleeding and spotting days was higher in the LNG-IUS 8 group than in the ENG implant group in the first 90-day RI. However, during the second 90-day RI, the number of bleeding and spotting days in the LNG-IUS 8 group reduced to a similar number to that of the ENG implant group. For the fourth 90-day RI, the mean number of bleeding days (excluding spotting) was 8.8 days in the ENG implant group and 6.5 days in the LNG-IUS 8 group. Furthermore, the median length of bleeding and spotting episodes by 28-day RI decreased more substantially with LNG-IUS 8 than with the ENG implant over time during use (17 days and 6 days [RI 1]; 5 days and 2 days [RI 12], for LNG-IUS 8 and the ENG implant, respectively).

For the fourth 90-day RI, the incidence of amenorrhea was 28.5% in the ENG implant group compared with 9.3% in the LNG-IUS 8 group, and the incidence of prolonged bleeding was 15.9% in the ENG implant group and 4.8% in the LNG-IUS 8 group (Table 4). In addition, the incidence of "normal bleeding" (bleeding that does not meet the World Health Organization criteria for amenorrhea, prolonged bleeding, frequent bleeding, infrequent bleeding, or irregular bleeding) in the LNG-IUS 8 group increased from 10.8% in RI 1 to >30% in

TABLE 4

Bleeding patterns according to World Health Organization criteria for menstrual bleeding patterns and 90-day RIs (modified intention-to-treat set[a]).

	LNG-IUS 8			ENG implant		
Pattern	**First 90-d RI**	**Second 90-d RI**	**Fourth 90-d RI**	**First 90-d RI**	**Second 90-d RI**	**Fourth 90-d RI**
Amenorrhea (%)[b]	0.0	3.9	9.3	3.8	20.1	28.5
Infrequent bleeding (%)[c]	20.5	16.6	24.8	37.3	33.2	28.9
Frequent bleeding (%)[d]	19.9	13.3	9.7	8.7	9.1	10.0
Prolonged bleeding (%)[e]	38.6	15.1	4.8	36.1	23.8	15.9
Irregular bleeding (%)[f]	48.6	29.9	24.5	34.1	31.0	27.8
Normal (none of the above) (%)[g]	10.8	35.3	31.4	15.3	6.0	4.8

Note: ENG = etonogestrel; LNG-IUS 8 = levonorgestrel intrauterine system total content 13.5 mg (average, ~8 μg/24 hours during the first year); RI = reference interval.
[a] Modified intention-to-treat set: all women for whom at least one placement/insertion attempt was made.
[b] Amenorrhea was defined as no bleeding/spotting throughout the 90-day RI.
[c] Infrequent bleeding was defined as one or two bleeding/spotting episodes per 90-day RI.
[d] Frequent bleeding was defined as more than five bleeding/spotting episodes per 90-day RI.
[e] Prolonged bleeding was defined as bleeding/spotting episodes lasting >14 days. Women with prolonged bleeding may also be included in one of the other categories (excluding amenorrhea).
[f] Irregular bleeding was defined as three to five bleeding/spotting episodes and fewer than three bleeding/spotting-free intervals of ≥14 days.
[g] Normal bleeding was defined as none of the above categories.

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subsequent RIs, whereas in the ENG implant group, the incidence decreased from 15.3% in RI 1 to 4.8% in RI 4.

Safety

Both LNG-IUS 8 and the ENG implant were associated with a favorable safety profile. The incidence of treatment-emergent adverse events (TEAEs) was 84.3% and 79.5% in the LNG-IUS 8 and the ENG implant groups, respectively. Among LNG-IUS 8 users, the most frequently reported TEAEs were dysmenorrhea (33.5%), uterine spasms (16.2%), procedural pain (13.6%), headache (11.3%), and acne (9.9%), whereas among ENG implant users, they were acne (15.5%), headache (12.3%), dysmenorrhea (12.3%), nasopharyngitis (9.2%), and cervical dysplasia (8.9%). Serious TEAEs were reported by 2.4% of women in each treatment group (9 events in each treatment group); two of these events (one EP and one pregnancy of unknown location [biochemical pregnancy]) were considered by the investigator to be study drug-related in the LNG-IUS 8 group and one of these events (cerebral infarction) was considered by the investigator to be study drug-related in the ENG implant group. The discontinuation rate owing to TEAEs was 15.4% and 21.8% in the LNG-IUS 8 and ENG implant groups, respectively. Study drug-related TEAEs leading to discontinuation are shown in Supplemental Table 1, available online. Adverse events of special interest are summarized in Supplemental Table 2, available online. Ovarian cysts were reported in 10 women in the LNG-IUS 8 group and 3 women in the ENG implant group. These were considered study drug-related in eight women in the LNG-IUS 8 group and in all three women in the ENG implant group.

DISCUSSION

During 12 months of use, significantly fewer women discontinued LNG-IUS 8 than discontinued with the ENG implant. The higher discontinuation rate with the ENG implant was mainly attributable to bleeding pattern alterations (11.5% of ENG implant users discontinued for this reason compared with 4.2% of LNG-IUS 8 users). Almost all discontinuations were associated with increased bleeding. This is consistent with the properties of the ENG implant, which are known to alter bleeding in an unpredictable manner (13, 14).

The lower discontinuation rate with LNG-IUS 8 reflects increased user satisfaction compared with ENG implant users at all study visits. Overall user satisfaction at Month 12/EOS was 80.2% in the LNG-IUS 8 group and 66.1% in the ENG implant group. User satisfaction with LNG-IUS 8 in this study was similarly high to that reported for LNG-IUS 20 in the US-based contraceptive CHOICE study. Of the LNG-IUS 20 users, 85.7% reported that they were "very satisfied" or "somewhat satisfied" with treatment after 12 months of use (15).

Furthermore, a prospective analysis examining use of LNG-IUS 20 and the ENG implant in women aged 20–35 years demonstrated a significantly higher 12-month continuation rate with LNG-IUS 20 than with the ENG implant (93% vs. 86%, respectively) (16). User satisfaction, assessed as the number of women reporting that they "definitely agree" or "somewhat agree" with the statement "I am satisfied with my contraceptive method," was also higher with LNG-IUS 20 than with the ENG implant after 12 months (80% using LNG-IUS 20 vs. 65% using the ENG implant) (16).

Although discontinuation rates were higher in the present study than with LNG-IUS 20 and the ENG implant in the study by Short et al. (16), overall satisfaction for both types of contraception was similar in both studies. This may be due to the higher proportion of young and nulliparous women in the present study who may more readily discontinue their contraceptive method than older, parous women, despite a similar level of user satisfaction.

In addition, a numerically higher proportion of LNG-IUS 8 users than ENG implant users stated a preference to continue treatment after study completion, and the percentage of women who were satisfied with their bleeding pattern at Month 12 was greater in the LNG-IUS 8 group than in the ENG implant group. These results suggest that LNG-IUS is an appealing contraceptive option.

During the 12-month study, the mean number of bleeding and spotting days per 90-day RI and the median length of bleeding and spotting episodes per 28-day RI decreased over time during use. The overall reduction was more substantial with LNG-IUS 8 than with the ENG implant in both cases. Bleeding patterns according to World Health Organization criteria (17) demonstrated that amenorrhea increased over time during use. However, in all RIs, more women experienced amenorrhea in the ENG implant group than in the LNG-IUS 8 group. The frequency of prolonged bleeding decreased over time with both study treatments, but more substantially with LNG-IUS 8. The increase in amenorrhea and decrease in prolonged bleeding over time were consistent with the expected bleeding profile for LNG-IUS 8 (6, 11). In addition, the proportion of women experiencing "normal bleeding" increased over time with LNG-IUS 8 use and decreased over time with the ENG implant.

Three pregnancies occurred during the 12-month study, all within the LNG-IUS 8 group, resulting in a PI of 0.9 compared with 0.0 for the ENG implant. However, this study was not powered to determine the PI accurately for either treatment, and the short relevant exposure times mean no definite conclusions regarding comparative efficacy of the two contraceptive methods can be made.

Both LNG-IUS 8 and the ENG implant were well tolerated, with no new or unexpected safety events observed. However, the number of study drug-related TEAEs that led to study discontinuation was higher in the ENG implant group (LNG-IUS 8, 14.7% vs. ENG implant, 21.0%). Ovarian cysts were reported in 10 women in the LNG-IUS 8 group and 3 women in the ENG implant group. Because reporting of ovarian cysts included women with complaints as well as those in whom cysts were detected without complaints on routine ultrasound at each study visit, the results may overstate the clinical importance of this event. Transvaginal ultrasound follow-up of 1,432 women during a 3-year phase III trial indicated that ovarian cysts associated with LNG-IUS 8 use are uncommon (18). The high spontaneous resolution rate for ovarian cysts reflects their physiologic/functional nature. More women in the ENG implant group than in the LNG-IUS 8 group reported acne as a TEAE (15.5% vs. 9.9%). The difference may be explained by the higher systematic activity of the progestin with the ENG implant compared with the LNG-IUS 8.

Although this was a large, randomized phase III study, some additional limitations to those outlined exist. The study was open-label and, because 75% of women were nulliparous, this precludes subgroup analysis according to parity. Women compared their bleeding intensity satisfaction with their own previous menstrual experience, meaning that results were subjective, and bleeding data at baseline were not captured. Therefore, it was difficult to fully interpret data in the first RI. Furthermore, women's perceptions of bleeding patterns in the first 90 days after placement may have been affected because approximately 45% of women in each treatment group switched from using oral contraception, and thus may have experienced lighter bleeding patterns before entering in the study. In addition, the number of bleeding and spotting days was not adjusted for women who prematurely discontinued.

In conclusion, during 12 months of use, discontinuation rates were significantly lower with LNG-IUS 8 compared with the ENG implant. The higher discontinuation rate with the ENG implant was mainly due to increased bleeding. Accordingly, almost twice as many women in the LNG-IUS 8 group than in the ENG implant group reported being "very/somewhat satisfied" with their bleeding pattern, which may have contributed to more women in the LNG-IUS 8 group than the ENG implant group reporting a preference to use their study treatment after the study. Both LNG-IUS 8 and the ENG implant were highly effective and neither method was associated with any new or unexpected safety events.

This study demonstrates that LARC methods are a suitable contraceptive option for nulliparous and parous women, and it provides further evidence that could be used by healthcare providers in contraceptive counseling. Increased use of LARC in the general population could substantially reduce unintended PRs.

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SUPPLEMENTAL MATERIAL

Exclusion Criteria

Further exclusion criteria were known or suspected pregnancy; current lactation; infected abortion or postpartum endometritis within 3 months before screening; distortion of the uterine cavity, which may, at the investigator's discretion, cause problems with placement, retention, or removal of levonorgestrel intrauterine system total content 13.5 mg (average, ~8 μg/24 hours during the first year) (LNG-IUS 8); acute, or a history of recurrent, pelvic inflammatory disease; abnormal genital bleeding of unknown origin; any acute lower genital infection (until successfully treated); or use of any long-acting injectable hormonal contraceptive within 10 months before randomization.

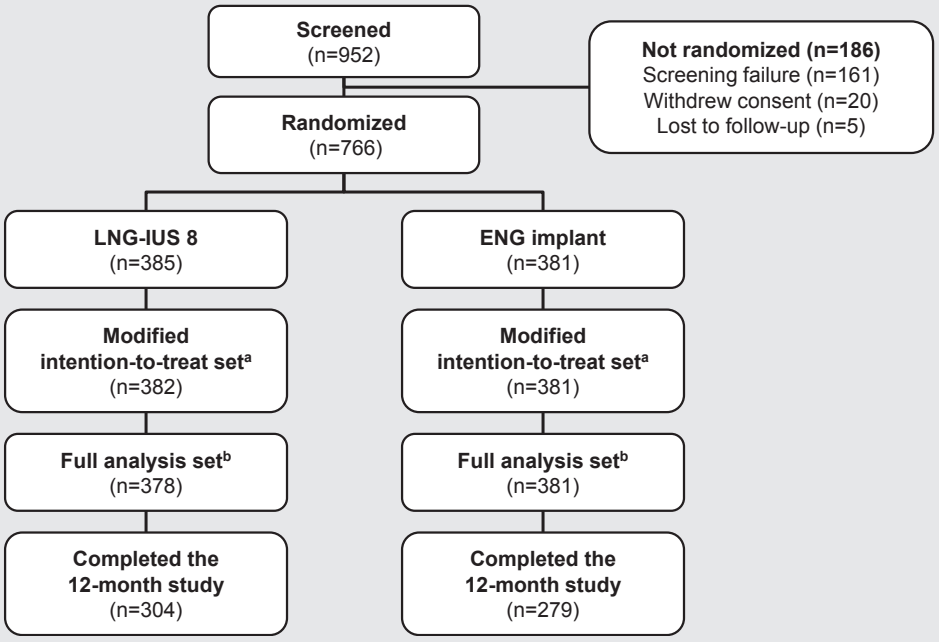
Study Treatment

For women not switching from another hormonal contraceptive, placement of LNG-IUS 8 or insertion of the etonogestrel (ENG) implant was performed during the first 5 days of the woman's menstrual cycle. For women switching from other hormonal contraceptives, the timing of placement of LNG-IUS 8 and insertion of the ENG implant was according to the local Summary of Product Characteristics for the reference drug (the ENG implant) (13).

Study Visits and Evaluation

Women answered two further questions at Months 6 and 12/EOS. The first of these questions was "If given a choice, after completion of the study, you would …". The response options were "continue with the study treatment," "use a different hormonal contraceptive," "use a different contraceptive method," "discontinue use of all types of contraceptives," "no need for contraceptive at this time," or "don't know." For the second question, "Since your last study visit, when you had menstrual bleeding, how satisfied were you with your menstrual bleeding pattern?", the response options were "very satisfied," "somewhat satisfied," "neither satisfied nor dissatisfied," "dissatisfied," "very dissatisfied," or "no menstrual bleeding during study treatment." The subset of women with absence of menstrual bleeding answered a further question, "How satisfied were you with the absence of menstrual bleeding?," using the response options "very satisfied," "somewhat satisfied," "neither satisfied nor dissatisfied," and "dissatisfied."

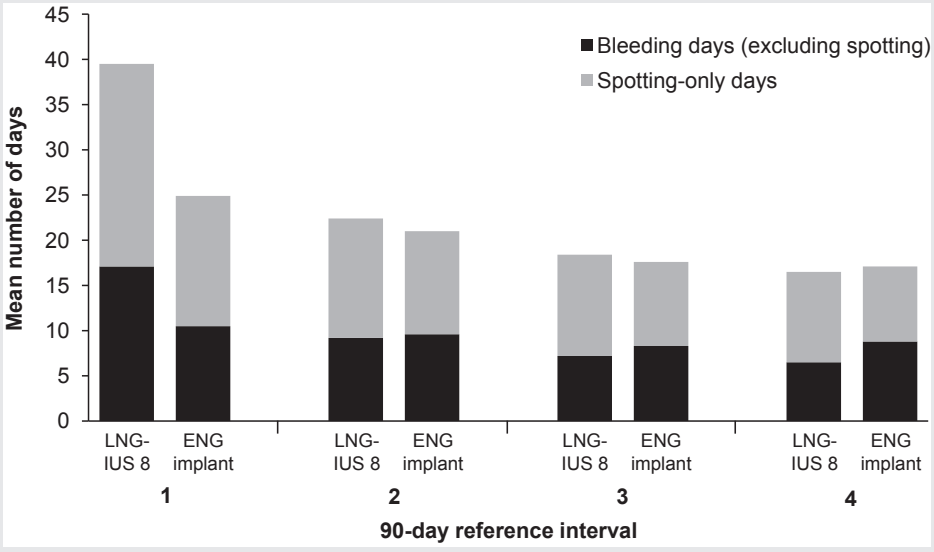
SUPPLEMENTAL FIGURE 1



Disposition of women in the study. [a]Modified intention-to-treat set: all women for whom at least one placement attempt was made. [b]Full analysis set: all women who had a successful placement/insertion. ENG = etonogestrel; LNG-IUS 8 = levonorgestrel intrauterine system total content 13.5 mg (average, ~8 μg/24 hours during the first year).

Apter. Comparing LNG-IUS 8 and the ENG implant. Fertil Steril 2016.

SUPPLEMENTAL FIGURE 2



Mean number of bleeding and spotting days by 90-day reference intervals[a] (modified intention-to-treat set[b]) in the LNG-IUS 8 and ENG implant groups. [a]The numbers of bleeding and spotting days were not recorded at baseline. [b]Modified intention-to-treat set: all women for whom at least one placement/insertion attempt was made. ENG = etonogestrel; LNG-IUS 8 = levonorgestrel intrauterine system total content 13.5 mg (average, ~8 μg/24 hours during the first year).

Apter. Comparing LNG-IUS 8 and the ENG implant. Fertil Steril 2016.

SUPPLEMENTAL TABLE 1

Incidence (> 1% in either treatment group) of study drug-related TEAEs leading to discontinuation of study treatment (modified intention-to-treat set[a]).

MedDRA preferred term	LNG-IUS 8 (n = 382)	ENG implant (n = 381)
Any study drug-related TEAE (%)	14.7	21.0
Acne	2.9	5.2
Dysmenorrhea	2.1	0.0
Abdominal pain, lower	1.6	0.0
Menometrorrhagia	1.0	1.8
Menorrhagia	0.8	3.7
Metrorrhagia	0.8	2.6
Vaginal hemorrhage	0.8	2.9
Weight increased	0.3	1.8
Mood altered	0.3	1.6
Libido decreased	0.0	1.3

Note: ENG = etonogestrel; LNG-IUS 8 = levonorgestrel intrauterine system total content 13.5 mg (average, ~8 μg/24 hours during the first year); MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event.

[a] Modified intention-to-treat set: all women for whom at least one placement/insertion attempt was made.

Apter. Comparing LNG-IUS 8 and the ENG implant. Fertil Steril 2016.

SUPPLEMENTAL TABLE 2

Adverse events of special interest (modified intention-to-treat set[a]).

Adverse event	LNG-IUS 8 (n = 382)	ENG implant (n = 381)
Ectopic pregnancy (n)	1	0
Expulsion (n)	3[b]	0
Uterine perforation (n)	0	Not relevant
Pelvic inflammatory disease (n)	1	0
Deeply inserted implant (n)	Not relevant	0
Implant site complications (n)	Not relevant	25
Implant site pruritus	–	9
Implant site pain	–	6
Implant site bruising	–	3
Implant site hematoma	–	2
Implant site erosion	–	1
Implant site irritation	–	1
Ovarian cysts (n)	10	3

Note: ENG = etonogestrel; LNG-IUS 8 = levonorgestrel intrauterine system total content 13.5 mg (average, ~8 μg/24 hours during the first year).
[a] Modified intention-to-treat set: all women for whom at least one placement/insertion attempt was made.
[b] All partial expulsions.

Apter. Comparing LNG-IUS 8 and the ENG implant. Fertil Steril 2016.