GYNECOLOGY

Levonorgestrel 52 mg intrauterine system efficacy and safety through 8 years of use

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BACKGROUND: Extending hormonal intrauterine system duration will allow users to have less need for procedures to provide long-term contraception.

OBJECTIVE: This study aimed to evaluate the efficacy and safety of the levonorgestrel 52 mg intrauterine system during years 7 and 8 of use.

STUDY DESIGN: A total of 1751 nulliparous and multiparous participants aged 16 to 45 years enrolled in a phase 3, multicenter trial to evaluate the efficacy and safety of the use of the Liletta levonorgestrel 52 mg intrauterine system for up to 10 years. Participants aged 36 to 45 years at enrollment underwent safety evaluation only. After the first year, we evaluated participants every 6 months for intrauterine system location confirmation and urine pregnancy testing at each visit. We assessed the Pearl Indices in years 7 and 8 and the life-table analysis for cumulative pregnancy rates through 8 years of use. For the primary efficacy analyses, all participants aged 16 to 35 years at enrollment were included through year 6; years 7 and 8 included only users aged ≤39 years at the start of each use year. Safety outcomes were assessed in all participants regardless of duration of use. We assessed amenorrhea rates, defined as no bleeding or spotting in the 90 days before the end of the year.

RESULTS: After intrauterine system placement, we followed 1568 participants aged 16 to 35 years and 146 participants aged 36 to 45 years. The 16- to 35-year-old participants included 986 (57.5%) nulliparous and 433 (25.3%) obese users. Overall, 569 participants started year 7, 478 completed year 7 (380 aged ≤39 years at beginning of year) and 343 completed year 8 (257 aged ≤39 years at beginning of year); 77 completed 10 years of use. Eleven pregnancies occurred over 8 years, 7 (64%) of which were ectopic. Two pregnancies occurred in year 7 (Pearl Index, 0.49; 95% confidence interval, 0.06—1.78), 1 in a participant with implantation 4 days after a desired removal; no pregnancies occurred in year 8. The cumulative life-table pregnancy rate in the primary efficacy population through year 8 was 1.32 (95% confidence interval, 0.69—2.51); without the postremoval pregnancy, the rate was 1.09 (95% confidence interval, 0.56—2.13). Two perforations (0.1%) occurred, none noted after year 1. Expulsion occurred in 71 (4.1%) participants overall, with 3 in year 7 and 2 in year 8. Pelvic infection was diagnosed in 16 (0.9%) participants during intrauterine system use, 1 each in years 7 and 8. Only 44 (2.6%) participants overall discontinued because of bleeding complaints (4 total in years 7 and 8) with rates per year of 0.1% to 0.5% for years 3 to 8. Amenorrhea rates were 39% at both years 7 and 8.

CONCLUSION: The levonorgestrel 52 mg intrauterine system is highly effective over 8 years of use and has an excellent extended safety profile. This report details the longest period of efficacy and safety data for continuous use of a levonorgestrel 52 mg intrauterine system for contraception.

Key words: 8 years, amenorrhea, contraception, efficacy, intrauterine device, intrauterine system, levonorgestrel, Liletta, safety

Introduction

Increasing the longevity of long-acting reversible contraception (LARC) methods benefits users by providing a longer window for pregnancy prevention without the need to undergo removal and replacement procedures, which have inherent risks and inconveniences. A longer duration of use is important for younger users who desire long-term birth prevention or spacing, and for persons who do not wish future childbearing by potentially decreasing the number of interventions until the end of the reproductive years. Extending the duration of use allows patients to forego unnecessary removal and reinsertion procedures when planning longer-term use.

Currently available LARC methods include intrauterine and subdermal implant products of which the intrauterine methods have a longer duration of use. The levonorgestrel 52 mg intrauterine system (IUS) was first marketed (Mirena, Bayer Healthcare, Whippany, NJ) with a 5-year duration without testing during development to identify the full duration of action potential. A large World Health Organization study demonstrated longer clinical efficacy, through 7 years, but with limited findings outside of China.[1] From 2000 to 2015, only 1 product was widely marketed and maintained this 5-year duration. In 2015, a second, prospectively studied branded product (Liletta, Medicines360, San Francisco, CA and AbbVie, North Chicago, IL [also other names outside the United States]) received initial approval for 3 years with plans to continue the efficacy trial for more than 5 years. In 2019, Liletta became the first hormonal IUS approved in the United States for 6 years. Bayer Healthcare initiated a study in 2016 to extend the Mirena duration with approval to 6 years in 2020 and to 7 years in 2021. In this report, we detail the clinical findings of the use of a levonorgestrel 52 mg IUS for 8 years.

Materials and Methods

The study methodology, institutional board review, sample size rationale, data analysis plans, and adverse event

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AJOG at a Glance

Why was this study conducted?

This study aimed to evaluate the efficacy and safety of the levonorgestrel 52 mg intrauterine system (IUS) for up to 8 years of continuous use.

Key findings

Pregnancy rates remained low with extended levonorgestrel 52 mg IUS use through 8 years with no significant safety findings with prolonged use. Amenorrhea rates remained relatively consistent around 40% for years 3 to 8.

What does this add to what is known?

This report details the current longest efficacy, safety, and amenorrhea data for continuous use of a levonorgestrel 52 mg IUS for contraception.

reporting criteria for this phase 3, multicenter trial (ACCESS IUS) have been published previously.[2,3] ACCESS IUS was designed to evaluate the efficacy and safety of the Liletta levonorgestrel 52 mg IUS for up to 10 years. The sponsor, Medicines360, designed the study and oversaw its conduct and also funded the trial and provided the study product free of charge to participants.

Briefly, investigators enrolled 16- to 45-year-old participants desiring a hormonal IUS for contraception. Participants had 4 scheduled visits in the first year of use and evaluations every 6 months thereafter with confirmation of the IUS location (by examination with ultrasonography as needed) and urine pregnancy testing at each visit. Telephonic discussions also occurred every 6 months beginning at 9 months of use. At each study visit or contact, study staff asked if the participant still considered the IUS as the primary contraceptive method.

The outcomes related to product approval for 3, 5, and 6 years have been published previously.[2−4] The efficacy and safety data for this current report includes all outcomes documented from the study start in December 2009 through the study end in March 2021, with specific focus on results after year 6. In this report, we evaluated outcomes for participants with at least 1 follow-up evaluation. Efficacy and bleeding analyses included participants with a maximum duration of follow-up of 8 years (96 months); safety analyses included any adverse events reported regardless of the duration of IUS use.

The primary outcome of an on-treatment pregnancy included any pregnancy with a conception date from the insertion date through 7 days after IUS discontinuation in participants aged 16 to 35 years at enrollment based on US Food and Drug Administration (FDA) criteria. We also evaluated outcomes using the European Medicines Agency (EMA) criteria, which includes the same population but defines on-treatment pregnancy to include those from the insertion date through to 2 days after IUS discontinuation. We calculated pregnancy rates primarily as the Pearl Index (pregnancies per 100 women-years), excluding the months in which participants used additional contraception; secondary efficacy outcomes include cumulative Pearl Indices over 6 years and life-table pregnancy rates calculated using the Kaplan-Meier method. Based on revised FDA guidance in 2020, we limited the pregnancy outcomes beginning in year 7 to participants aged ≤39 years at the start of each use year. We assessed amenorrhea rates, defined as no bleeding or spotting in the 90 days before the end of the year, and safety evaluations in all enrolled participants.

We compared the characteristics of participants entering years 7 and 8 with the characteristics of those at enrollment using Fisher exact, chi-square, and *t* test analyses as appropriate. Data were analyzed using SAS Software version 9.3 (SAS Institute, Inc., Cary, NC) with a *P* value of <.05 being considered significant.

Results

Of the 1714 participants who received a levonorgestrel 52 mg IUS in this trial, 576 participants started year 7, 478 completed year 7 (380 aged ≤39 years at beginning of year), and 343 completed year 8 (257 aged ≤39 years at beginning of year). The demographic characteristics are presented in Table 1. The overall population characteristics of the participants entering years 7 and 8 compared with the participant characteristics at enrollment did not differ except for slightly fewer Hispanic-identifying persons entering year 7 (but not year 8). The 16- to 35-year-old participants initially included 986 (57.5%) nulliparous and 433 (25.3%) obese users; entering years 7 and 8, the proportions remained similar for nulliparous (336 [58.3%] and 276 [57.9%], respectively) and obese (147 [25.5%] and 120 [25.2%], respectively) participants.

Eleven pregnancies occurred over 8 years, 7 (64%) of which were ectopic (Supplemental Table). Two pregnancies occurred in year 7 and none in year 8 (Table 2). In year 7, the pregnancy rates for the 499 participants entering year 7 who were ≤35 years at study entry (Pearl Index, 0.46; 95% confidence interval [CI], 0.06−1.66 pregnancies per 100 women-years) were similar to the calculated rates when limited to the 465 participants who were aged ≤39 years at the beginning of study year (Pearl Index, 0.49; 95% CI, 0.06−1.78 pregnancies per 100 women-years). With no pregnancies in year 8 and limiting the evaluation group to only persons aged ≤39 years at the beginning of the study year had no significant impact.

The year 7 pregnancies included 1 ectopic pregnancy with the IUS in the uterus and 1 with intrauterine implantation based on transvaginal ultrasonography 4 days after IUS removal. This postremoval pregnancy was the only postremoval pregnancy that occurred during the trial. The life-table pregnancy rate through year 8 was 1.32% (95% CI, 0.69−2.51); without the postremoval

pregnancy (in line with EMA efficacy calculation guidelines), the rate was 1.09% (95% CI, 0.56−2.13).

Adverse events and reactions included any outcomes up to 10 years after IUS placement with 83 and 77 participants completing 9 and 10 years of use, respectively (Table 3). The most commonly reported events over 8 or more years of use among the 1714 participants receiving an IUS were vulvovaginal infections with bacteria (n=315, 18.4%) or yeast (n=304, 17.7%) and urinary tract infections (n=314, 18.3%). These events also represented those most commonly reported in years 7 and 8 (Table 3). A pelvic infection was diagnosed in 16 (0.9%) participants during IUS use with 4 occurring during the first 6 months, 4 occurring during the second 6 months, and 0 to 2 per year thereafter, including 1 each in years 7 and 8. Chlamydia and gonorrhea test results at the time of diagnosis for persons with infections in years 7 and 8 were negative.

Early discontinuation most frequently occurred for participants seeking pregnancy (n=315, 18.4%) or for study-specific reasons (n=572, 33.4%) and not for complications associated with IUS use or the desire to use another contraceptive method. Most commonly, these study-specific reasons included loss to follow-up or withdrawal of consent (n=347, 20.2%) and relocation far from a study site (n=117, 6.8%). About one-fifth (n=344, 20.1%) of participants over a period of up to 10 years of follow-up discontinued use because of an adverse event, most frequently expulsion (n=71, 4.1%) and bleeding complaints (n=44, 2.6%). Most expulsions (n=50, 71%) occurred during year 1. In years 7 and 8, 3 of 576 (0.5%) and 2 of 477 (0.4%) participants experienced expulsion, respectively. Overall, these events included 29 (1.7%) complete and 42 (2.5%) partial expulsions. Expulsion occurred in 24 of 986 (2.4%) nulliparous and 47 of 728 (6.5%) parous participants (P=.0001). Two perforations (0.1%) occurred, with none noted after year 1. No cases of myometrial embedment of an IUS arm were reported.

Amenorrhea rates in years 7 and 8 remained stable when compared with previous years with rates of 37% to 42% from years 3 through 8 (Figure). Annual discontinuation for a bleeding complaint rate remained low (0.1% to 0.5%) in years 3 through 8 (Table 4).

TABLE 1
Demographics at enrollment, entering year 7 and entering year 8 for participants in a phase 3 study who had successful placement of a levonorgestrel 52 mg intrauterine system

Characteristic	Enrollment N=1714	Entering year 7 n=576	Entering year 8 n=477
Age (y)[a]	27.3±5.7	34.4±6.3	35.7±6.4
≤35	1568 (91.5)	346 (60.1)	249 (52.2)
36−39	85 (5.0)	119 (20.7)	100 (21.0)
≥40	61 (3.6)	111 (19.3)	128 (26.8)
Ethnicity			
Hispanic or Latina	251 (14.6)	65 (11.3)[b]	53 (11.1)
Race[c]			
American Indian or Alaska Native	21 (1.2)	6 (1.0)	5 (1.0)
Asian	67 (3.9)	28 (4.9)	25 (5.2)
Black or African American	225 (13.2)	66 (11.5)	48 (10.1)
Native Hawaiian or Other Pacific Islander	6 (0.4)	1 (0.2)	0
White	1342 (78.5)	462 (80.2)	389 (81.6)
Multiple races indicated	49 (2.9)	12 (2.1)	9 (1.9)
Body mass index (kg/m^2)[d]	26.9±6.8	27.1±6.9	27.2±7.1
Obese (≥30.0)	433 (25.3)	147 (25.5)	120 (25.2)
Partner status			
Lives with partner	1003 (58.5)	340 (59.0)	290 (60.8)
Parity			
Nulliparous	986 (57.5)	336 (58.3)	276 (57.9)
Marital status			
Never married	1081 (63.1)	365 (63.4)	299 (62.7)
Married	478 (27.9)	164 (28.5)	138 (28.9)
Divorced or separated or widowed	155 (9.0)	47 (8.2)	40 (8.4)

Data are presented as number (percentage) or mean±standard deviation.

[a] Efficacy before year 7 included all participants aged ≤35 years at enrollment; efficacy in years 7 and 8 only included participants aged ≤39 years at the beginning of the use year; [b] Significance of P=.04 when compared with enrollment population; [c] Data missing for 4 participants at enrollment and 1 participant at the beginning of years 7 and 8; [d] Data missing for 4 participants at enrollment and 1 participant at the beginning of year 7.

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Comment

Principal findings

The levonorgestrel 52 mg IUS remains highly effective with approximately 1% of users becoming pregnant through up to 8 continuous years of use. No new safety concerns arose with extended use. Amenorrhea rates remained relatively constant, at approximately 40% of the user population from years 3 to 8 with very low rates of discontinuation for bleeding (2.6%).

Results in the context of what is known

Limited data have been published on the efficacy of the levonorgestrel 52 mg IUS beyond 6 years of use and no data are

TABLE 2
Pregnancy outcomes in years 7 and 8 of levonorgestrel 52 mg intrauterine system use

Population	Year	Number starting year	Number of 28-d cycles	Number of pregnancies, total (ectopic)	Pearl Index[a] (pregnancies per 100 women-years)	Life-table (cumulative %)
≤35 y old at enrolment[b]	7	499	5646	2 (1)[c]	0.46 (0.06–1.66)	1.30 (0.69–2.47)
	8	405	4299	0	0.00 (0.00–1.12)	1.30 (0.69–2.47)
≤35 y old at enrollment, exclude 7-y pregnancy with conception 4 d after removal[d]	7	499	5646	1 (1)	0.23 (0.01–1.28)	1.09 (0.56–2.11)
	8	405	4299	0	0.00 (0.00–1.12)	1.09 (0.56–2.11)
≤39 y old at beginning of study year[b]	7	465	5280	2 (1)[c]	0.49 (0.06–1.78)	1.32 (0.69–2.51)
	8	349	3657	0	0.00 (0.00–1.31)	1.32 (0.69–2.51)
≤39 y old at beginning of study year, exclude 7-y pregnancy with conception 4 d after removal[d]	7	465	5280	1 (1)	0.25 (0.01–1.37)	1.09 (0.56–2.13)
	8	349	3657	0	0.00 (0.00–1.31)	1.09 (0.56–2.13)

IUS, intrauterine system.

[a] Individual year; [b] Includes all conceptions with IUS use or within 7 days of discontinuation (US Food and Drug Administration criteria); [c] One pregnancy in year 7 with conception 4 days after IUS removal; [d] Includes all conceptions with IUS use or within 2 days of discontinuation (European Medicines Agency criteria).

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available for more than 7 years of continuous use of a single IUS. One World Health Organization trial evaluated participants through 7 years that included participants >35 years at enrollment.[1] The study enrolled 1884 parous persons with more than half (1062 [56%]) of those enrolled at sites in China. Of the 601 participants who reached 7 years of continuous use, the proportion was not evenly distributed by sites, with only 138 (23%) from non-Chinese sites. No pregnancies occurred after year 5; however, of the limited number of persons reaching 7 years of use, it is unclear how many were ≥35 years at enrollment.

The continued safety with extended use of a single IUS is an important finding for clinicians and patients. Prolonged continuous use is known to be safe based on data from other intrauterine devices (IUDs), such as the approved 10-year duration of the copper T380A.[5] As expected in a sexually active population, pelvic infections occurred, and we were reassured that the number of new infections per year remained relatively low. Andersson et al[6] reported a 0.6% pelvic infection rate over 5 years of levonorgestrel 52 mg IUS use among parous patients with a mean age of >30 years enrolled in a trial in the 1980s. Given the population differences between that study and ours, we are reassured by our continued low infection rate of 0.9% during up to 10 years of use.

Before the ACCESS IUS trial, very little data have been available on amenorrhea rates beyond the first year of use in a general population. A single study evaluated bleeding patterns in persons who used a levonorgestrel 52 mg IUS for 5 years and then had a removal and replacement procedure.[7] That study evaluated 170 persons (mean age, 39 years) with 51 to 57 months of IUS use for contraception or heavy menstrual bleeding at study entry. Amenorrhea rates at study entry were 30% for the 90 days before study entry, 34% at the end of 1 year (sixth total year of use), and ranged from 44% to 49% over the next 4 years of use.[8,9] Given the slightly older age of their study population when compared with the ACCESS IUS trial, our continued rate of approximately 40% with continuous use is clinically similar.

Clinical implications

Pharmacokinetic evaluations from the ACCESS IUS study demonstrated release rates of 9.8 μg/day after 5 years of use with 26.3 mg of levonorgestrel remaining in the IUS.[10] The release rate and remaining levonorgestrel content exceeded the initial values of lower dose levonorgestrel IUS products, providing support for the ability of these products to have a longer duration of action. This study represents the longest continuous prospective evaluation of an IUS, demonstrating high efficacy through 8 years of use. Furthermore, randomized trials have demonstrated no difference in systemic side effects over 3 years of use when comparing the levonorgestrel 52 mg IUS with lower-dose products.[7] In addition, the levonorgestrel 52 mg IUS has higher rates of amenorrhea and infrequent bleeding and less irregular bleeding over the first few years of use

than lower-dose products.[11] We found that these favorable bleeding outcomes persisted through 8 years of use with stable amenorrhea rates and no clinically relevant change in annual discontinuation for bleeding complaints with extended use.

Notably, perforations in this long-term study were noted in the first year and were related to the placement process.[2] In addition, expulsion occurred most frequently in the first year after placement. Taken together, a more limited label-stated duration could lead to exposure of more patients to perforation and expulsion risks and pain with removal and reinsertion procedures. The IUD is the third most commonly used reversible contraceptive in the United States and is used by 15.9% of contraceptors[12]; as such, studies that support the longest duration of use, especially for a highly effective method, can have a huge impact on the contracepting population.

Research implications

The ACCESS IUS study was set up to provide complete data over 10 years of use, effectively doubling the originally approved duration of use. Our analyses demonstrated negligible differences in the efficacy outcomes whether the data were restricted to persons <40 years at the time of assessment or whether the data included all persons ≤35 years at the time of enrollment. The data presented suggest that the levonorgestrel 52 mg IUS would continue to be effective beyond 8 years. However, the feasibility of creating a large trial with enough young participants who would not discontinue use for desiring pregnancy may be impractical.

Strengths and limitations

The ACCESS IUS trial is a large phase 3 intrauterine contraceptive study, enrolling only participants in the United States and including a broad range of persons requesting contraception, more than half of whom were nulliparous. However, including a large proportion of young participants without children in a long-term study leads to high rates of discontinuation over time because of desired fertility, leaving a population in the later years of the study that are, on average, older. Although 91% of enrollees were ≤35 years at enrollment, 60% were ≤35 years at the start of year 7 and 52% were ≤35 years at the start of year 8. This natural and expected aging of the study

TABLE 3
Adverse events with a frequency ≥5.0% over a period of up to 10 years in US persons and potentially related to levonorgestrel 52 mg intrauterine system use

Adverse event	Total number of participants reporting at least 1 event during study (N=1714)	Total number of participants reporting at least 1 event during years 7–8 (n=576)[a]
Vulvovaginal mycotic infection	353 (20.6)	42 (7.3)
Vaginal bacterial infection	337 (19.7)	39 (6.8)
Acne	271 (15.8)	7 (1.2)
Nausea or vomiting	183 (10.7)	5 (0.9)
Breast tenderness or pain	177 (10.3)	7 (1.2)
Headache[b]	176 (10.3)	8 (1.4)
Abdominal discomfort or pain	175 (10.2)	5 (0.9)
Anxiety	168 (9.8)	11 (1.9)
Dyspareunia	168 (9.8)	5 (0.9)
Depression	160 (9.3)	14 (2.4)
Pelvic discomfort or pain	152 (8.9)	10 (1.7)
Dysmenorrhea	128 (7.5)	22 (3.8)
Mood changes	114 (6.7)	2 (0.3)
Back pain	113 (6.6)	11 (1.9)
Weight increase	106 (6.2)	2 (0.3)
Vaginal discharge	101 (5.9)	7 (1.2)

Data are reported as number (percentage).

IUS, intrauterine system.

[a] Number represents participants starting year 7 of IUS use; [b] Does not include reports of migraine headaches.

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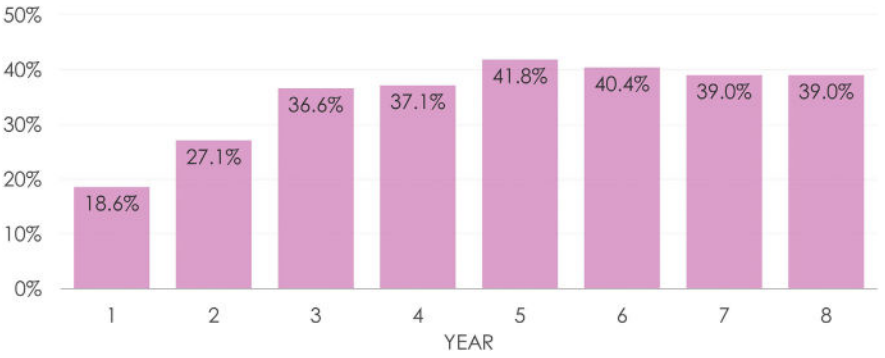
FIGURE
Amenorrhea rates over 8 years of levonorgestrel 52 mg IUS use



This figure shows the annual amenorrhea rate, defined as no bleeding or spotting in the 90 days before the end of the assessment year.

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TABLE 4
Discontinuation for bleeding complaints during 8 years of levonorgestrel 52 mg intrauterine system use

Year	Number starting treatment year[a]	n (%)
1	1714	17 (1.0)
2	1401	13 (0.9)
3	1149	5 (0.4)
4	965	2 (0.2)
5	808	2 (0.2)
6	688	1 (0.1)
7	576	3 (0.5)
8	477	1 (0.2)

Only 1 participant discontinued for amenorrhea (in year 2).

[a] Includes all enrolled participants receiving a levonorgestrel 52 mg intrauterine system (16–45 years at enrollment).

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population led to fewer participants being eligible for the FDA's revised efficacy analyses requirements for years 7 and 8. However, discontinuation seems to have occurred proportionately by age because the average age of the population at years 7 and 8 were 7 and 8 years higher, respectively, than at enrollment. Overall, the demographics of the population at years 7 and 8, other than age, still primarily matched the demographics at enrollment, meaning that the findings remain generalizable across the US population.

Conclusions

These results demonstrated that the levonorgestrel 52 mg IUS is highly effective over 8 continuous years of use and that it has an excellent extended safety profile with up to 10 years of use. The 8-year life-table pregnancy rate during IUS use was approximately 1%. The levonorgestrel 52 mg IUS offers the longest duration of use of any hormonal intrauterine contraceptive from a single procedure, decreasing the need for removal and insertion procedures for longer contraceptive protection. ■

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Participant data beyond what is presented in the manuscript will not be provided.

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SUPPLEMENTAL TABLE

Pregnancy outcomes through 8 years of levonorgestrel 52 mg intrauterine system use in participants ≤35 years at enrollment

Year	Number of 28-d cycles	Number of pregnancies,[a] total (ectopic)	Pearl Index[b] (pregnancies per 100 women-years)	Life-Table (cumulative %)
1[c]	17,175	2 (1)	0.15 (0.02–0.55)	0.14 (0.04–0.57)
2	14,205	4 (3)	0.37 (0.10–0.94)	0.50 (0.22–1.10)
3	11,760	1 (1)	0.11 (0.00–0.62)	0.60 (0.29–1.27)
4	9891	1 (1)	0.13 (0.00–0.73)	0.73 (0.36–1.48)
5	8337	1 (0)	0.16 (0.00–0.87)	0.89 (0.45–1.74)
6	6916	0	0.00 (0.00–0.69)	0.89 (0.45–1.74)
7[d]	5646	2 (1)	0.46 (0.06–1.66)	1.35 (0.71–2.58)
8	4299	0	0.00 (0.00–1.12)	1.35 (0.71–2.58)

IUS, intrauterine system.

[a] Includes all conception with IUS use or within 7 days of discontinuation; [b] Individual year; [c] One pregnancy following perforation and 1 pregnancy following complete expulsion—both in year 1; [d] One pregnancy in year 7 with conception 4 days after IUS removal.

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