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Three-year efficacy and safety of a new 52-mg levonorgestrel-releasing intrauterine system^{☆,☆☆}

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Abstract

Objective: To assess 3-year data on the efficacy and safety of a new 52-mg levonorgestrel intrauterine contraceptive (LNG20) designed for up to 7 years use.

Study Design: Nulliparous and parous women aged 16–45 years at enrollment with regular menstrual cycles and requesting contraception were enrolled in an open-label, partially randomized trial to evaluate LNG20. The primary outcome was pregnancy rate for women aged 16–35 years calculated as the Pearl Index. Women aged 36–45 years received LNG20 for safety evaluation only. All participants had in-person or phone follow-up approximately every 3 months during the study.

Results: A total of 1600 women aged 16–35 years and 151 women aged 36–45 years agreed to LNG20 placement, including 1011 (57.7%) nulliparous and 438 (25.1%) obese women. Successful placement occurred in 1714 (97.9%) women. Six pregnancies occurred, four of which were ectopic. The Pearl Index for LNG20 was 0.15 (95% CI 0.02–0.55) through Year 1, 0.26 (95% CI 0.10–0.57) through Year 2, and 0.22 (95% CI 0.08–0.49) through Year 3. The cumulative life-table pregnancy rate was 0.55 (95% CI 0.24–1.23) through 3 years. Expulsion was reported in 62 (3.5%) participants, most (50 [80.6%]) during the first year of use. Of women who discontinued LNG20 and desired pregnancy, 86.8% conceived spontaneously within 12 months. Pelvic infection was diagnosed in 10 (0.6%) women. Only 26 (1.5%) LNG20 users discontinued due to bleeding complaints.

Conclusion: The LNG20 intrauterine system is highly effective and safe over 3 years of use in nulliparous and parous women.

Implications statement: A new 52-mg levonorgestrel-releasing intrauterine system is effective and safe for nulliparous and parous women for at least 3 years.

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Keywords: Contraception; Intrauterine device; Levonorgestrel; Liletta

1. Introduction

In the United States, more than half (51%) of approximately 6.6 million pregnancies each year are unintended with 40% of unintended pregnancies ending in abortion [1]. Women who use copper intrauterine devices (IUD), hormonal intrauterine systems (IUS) and contraceptive implants have substantially lower rates of unintended pregnancy than women using other methods of reversible contraception [2]. Intrauterine contraceptives are used by

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more than 150 million women worldwide [3]. In the U.S., however, only 7.7% of women practicing contraception use intrauterine products [4]. Intrauterine contraceptives can prevent pregnancy for several years, with efficacy equivalent to contraceptive sterilization [5]. When intrauterine contraceptives are removed, the return to fertility is rapid [6–8]. Overall, intrauterine contraceptives are among the safest and most cost effective contraceptive methods [9].

Socioeconomic level has an important relationship to unintended pregnancy. Women with household incomes below 200% of the Federal Poverty Level have a 5.3-fold greater risk of unintended pregnancy than women with higher incomes [1]. This disparity has increased from a 2.5-fold difference in 1994 [1,10]. Women of lower socioeconomic levels may have particular difficulty in accessing highly effective contraceptives due to cost or lack of insurance [11].

ACCESS IUS (A Comprehensive Contraceptive Efficacy and Safety Study of an IUS) was designed to assess efficacy and safety of a branded levonorgestrel-releasing IUS (LNG20) for up to 7 years of contraception in a diverse population of women. This study was conducted by Medicines360, a non-profit women's health pharmaceutical company founded to expand access to quality women's health products including LNG20. This report includes the initial data submitted to the U.S. Food and Drug Administration (FDA) for a 3-year indication of use and includes efficacy data based on participation for up to 36 months through 19 December 2014 and safety data, regardless of total duration of use, for all participants through 30 May 2014.

2. Materials and methods

The ACCESS IUS multicenter, Phase 3, open-label clinical trial was conducted at 29 clinical sites in the United States, including public, private and university centers. The study was approved by a central or local Institutional Review Board for each center, as applicable. All women signed written informed consent before study participation. The study was registered with Clinicaltrials.gov, identifier number NCT00995150. An independent data-safety monitoring committee reviewed the data every 6 months.

Enrollment began in December 2009 as a randomized trial comparing LNG20 (LilettaTM; Medicines360, San Francisco, CA, USA, and Actavis, Parsippany, NJ, USA; LilettaTM is a trademark of Odyssea Pharma SPRL [Belgium], an Actavis affiliate) to the currently marketed levonorgestrel 52 mg IUS (Mirena[®]; Bayer Healthcare, Whippany, NJ, USA) in a 4:1 ratio. LNG20 has a T-frame measuring 32 by 32 mm with a release rate-controlling membrane over a reservoir containing 52 mg levonorgestrel. Mirena was included as an informational safety comparator as initially required for an intended non-U.S. filing without plans for formal or informal comparisons. After enrolling 159 of the planned 400 Mirena participants, it was determined that this comparator group would no longer be

needed for the non-U.S. filing; thus, further enrollment was limited to LNG20 only. Because the Mirena cohort was not large enough for effectiveness calculations or statistically meaningful comparisons, those data are not presented.

Healthy, non-pregnant, sexually active (at least four times monthly), nulliparous and parous women aged 16–45 years (inclusive) with regular menstrual cycles (21–35 days when not using hormones and with a variation of typical cycle length of no more than 5 days) were invited to participate. Exclusion criteria ensured good general health, potential fertility and low risk with IUS use and did not include any restrictions on weight or body mass index (See Appendix 1).

At the screening visit and after signing informed consent, participants provided a medical history and underwent blood testing for hemoglobin level and liver and kidney function and a pelvic exam to ensure all study criteria were met. Women without a documented normal Pap test within the past 18 months had testing performed. All participants had Chlamydia testing; women who had no gonorrhea testing since starting their current sexual relationship also had gonorrhea testing. Women with a positive Chlamydia or gonorrhea test at baseline or during the study were treated with oral antibiotics without requirement for IUS removal.

Enrollment and IUS placement could occur on the same day as the screening procedures. IUS placement was not delayed to obtain Chlamydia or gonorrhea testing results. In general, IUS placement could occur at any time in eligible participants using a hormonal contraceptive or intrauterine contraceptive (which was to be removed prior to study IUS placement) or during the first 7 days of the menstrual cycle for women using other contraceptive methods. Study staff contacted an Interactive Voice Response System which assigned the IUS to be placed and tracked subject enrollment centrally. A statistician with no clinical role in conduct of the study performed the randomization initially used for product assignment. IUS placement was only attempted in women if the uterus was successfully sounded to 5.5 cm or more. Up to two placement attempts could occur within 30 days of signing consent. Information on how to check for the IUS strings was provided but the women were not required to routinely check the strings. Participants received a diary for daily recording of spotting, bleeding, cramping and other contraceptive use for the first 24 months; thereafter, they only recorded additional contraceptive use.

Follow-up visits were scheduled at 1, 3 and 6 months after LNG20 placement and every 6 months thereafter to assess adverse events, changes in sexual partner, medical history, concomitant medication use and whether LNG20 was still the primary method of contraception. Each follow-up visit included a review of diaries, a urine pregnancy test and measurement of vital signs. IUS presence was confirmed by palpation or direct visualization of the strings; women with missing strings underwent transvaginal ultrasonography to confirm IUS presence at that visit and at subsequent annual visits. Partial IUS expulsion was defined a priori as visual evidence of the lower portion of the IUS stem protruding

through the cervical os, or complaints of increased bleeding and/or cramping with the presence of the IUS in the lower uterine segment or cervix. Pap testing [12] and sexually transmitted disease screening [13] were performed when clinically indicated; hemoglobin testing was repeated at month 12 and study exit. Women who opted to discontinue LNG20 use, experienced expulsion or were diagnosed with pregnancy had a discontinuation office visit with the same evaluations and IUS removal (if still in place). Starting at Month 9, telephone contacts occurred 3 months after each clinic visit to ask the same questions as at study visits.

A follow-up visit was scheduled 30–43 days after discontinuing the study treatment for safety assessments. Further follow-up was conducted up to 3 months for return of spontaneous menses in women who elected to start a non-hormonal contraceptive method or no contraception. Women who desired pregnancy were followed up to 12 months to assess return to fertility.

The sample size was selected to meet U.S. FDA criteria for product approval based on efficacy (Pearl Index) and having at least 200 women reach the desired duration of use among women 16–35 years old at study entry. The Pearl Index at each year was required to have a two-sided 95% CI such that the upper limit of the CI was no more than one point greater than the Pearl Index point estimate. To meet these requirements, 1600 women were enrolled in the main LNG20 study arm assessing pregnancy and safety. An additional 151 women 36–45 years were enrolled in a non-randomized cohort for LNG20 safety only.

The primary outcome was on-treatment pregnancy, which was defined as any pregnancy with a date of conception beginning with the day of LNG20 placement and through 7 days after IUS discontinuation. Pregnancies were identified through subject query, urine testing and confirmatory serum pregnancy testing. A transvaginal ultrasound was performed for pregnancy dating and to verify IUS presence. On-treatment pregnancies were followed to completion.

Pregnancy rates were calculated as the Pearl Index (number of pregnancies per 100 woman-years) for individual years and cumulatively over three years including only months during which women did not report any other contraceptive use. If, however, a pregnancy occurred during a month with additional contraceptive use, that month was included in the denominator. Pregnancies among women in whom an expulsion was not identified prior to the pregnancy diagnosis were included as product failures. Secondary efficacy outcomes included life-table failure rates calculated using the Kaplan-Meier method, and Pearl Index and life-table analyses without exclusion of months with other contraceptive use.

Investigators at each study site assessed the severity of adverse events (safety outcomes) and their relationship to the IUS or to the placement or removal procedure. Adverse events were organized into standardized terms using the MedDRA (Medical Dictionary for Regulatory Activities) in accordance with the International Conference on Harmoni-

sation of Technical Requirements for Registration of Pharmaceuticals for Human Use. Pelvic infection included all women diagnosed by a clinician with endometritis or pelvic inflammatory disease (PID). Fisher exact tests were used when appropriate. Data were analyzed using SAS® Software Version 9.3 (SAS Institute, Inc., Cary, NC, USA).

3. Results

Of the 1751 who enrolled and were assigned to receive LNG20, 1600 were 16–35 years old and 151 were 36–46 years old (Fig. 1). Demographic characteristics of the study population appear in Table 1. Of note, 171 (9.8%) women were using intrauterine contraception at enrollment, which was removed prior to study product placement. Successful placement occurred in 1714 (97.9%). Fifteen (0.9%) participants did not have product placement attempted because the uterus could not be sounded ($n=9$), the uterus sounded to less than 5.5 cm ($n=2$), or problems occurred that were unrelated to the product or inserter ($n=4$). Thus, the successful LNG20 placement rate amongst those women who had product placement attempted was 98.7%.

Among women 16–35 years of age, 31971 women-months (34711 women-cycles) of LNG20 use are included in the efficacy analysis. For the safety analysis of participants 16–45 years, 1412, 572 and 383 women had completed 1, 2 and 3 years of product use, respectively (Fig. 1). Overall, 614 (39.1%) 16–35 year olds and 47 (32.1%) 36–45 year olds had discontinued study participation, most frequently for an adverse event ($n=215$, 12.3%), lost to follow-up or withdrawal of consent ($n=137$, 7.9%) or desiring pregnancy ($n=97$, 5.5%).

Two pregnancies occurred in Year 1 and four in Year 2. The pregnancies in Year 1 included one intrauterine pregnancy after LNG20 expulsion and one ectopic pregnancy associated with a perforation. The pregnancies in Year 2 included three ectopic pregnancies and one intrauterine pregnancy which resulted in an early pregnancy failure. Pregnancies occurred in two nulliparous and four parous participants. The Pearl Index for LNG20 is 0.15 (95% CI 0.02–0.55) through year one, 0.26 (95% CI 0.10–0.57) through year two, and 0.22 (95% CI 0.08–0.49) through year 3. The ectopic pregnancy rate through 3 years is 0.12 per 100-women years. Life-table analysis of 16–35 year olds yielded a pregnancy rate of 0.14 (95% CI 0.04–0.57) through 1 year and 0.55 (95% CI 0.24–1.23) through 3 years. No pregnancies occurred in LNG20 users 36–45 years of age.

Adverse reactions with a frequency of 5% or greater are reported in Table 2. At least one adverse event was noted in 1333 (83.3%) of 16–35 year olds and 131 (86.8%) of 36–45 year olds. Few adverse events were considered by the investigator to be related to LNG20 with an incidence >2% (Table 3). The most common adverse events leading to discontinuation were expulsion (3.5%), bleeding complaints (1.5%), acne (1.3%) and mood swings (1.3%). Other adverse

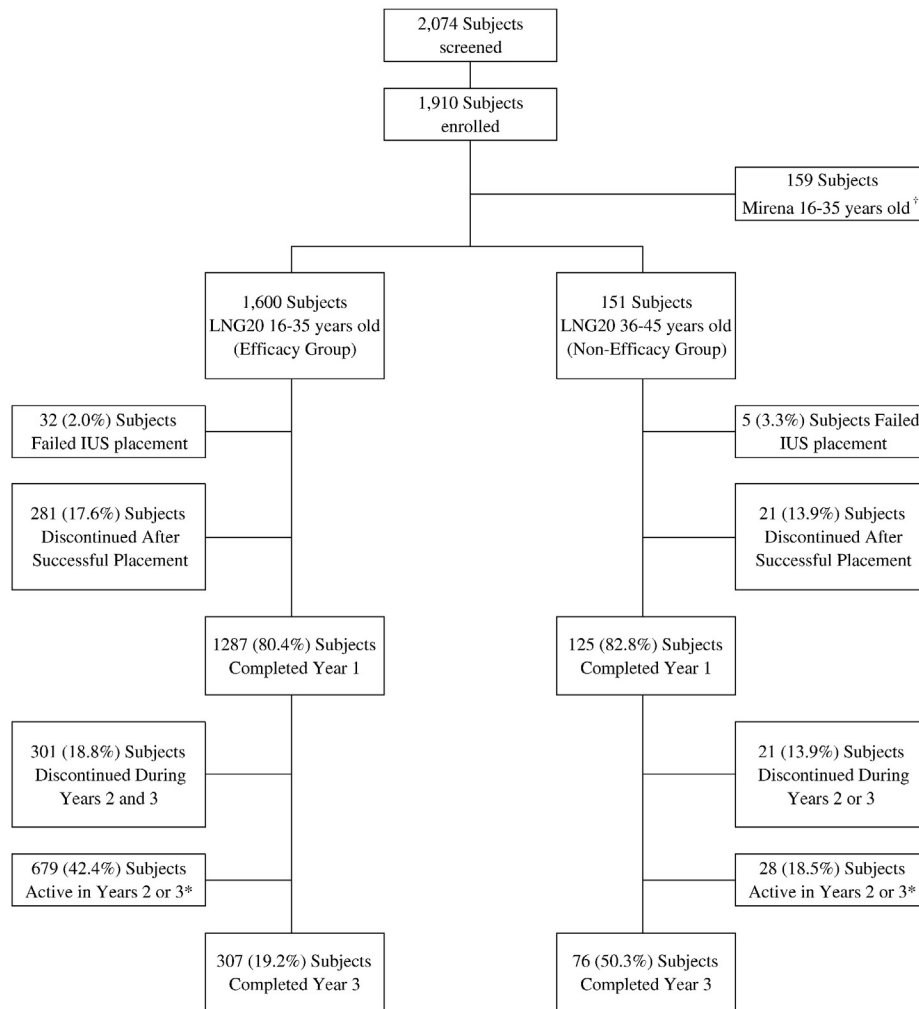


Fig. 1. Disposition of participants in a phase 3 study investigating LNG20*. * The study is still ongoing; not all active participants have completed 2 years and 3 years of participation. † Enrollment was initiated in December 2009 as a randomized trial comparing LNG20 to the currently marketed levonorgestrel 52 mg IUS (Mirena®, Bayer Healthcare, Whippany, NJ, USA) in a 4:1 ratio. Mirena enrollment was discontinued early in the trial after it was determined that this comparator group would no longer be needed for non-U.S. approval submissions. Data from the Mirena cohort are not presented because the group was not large enough for effectiveness calculations or statistically meaningful comparisons.

events related to discontinuation had an incidence of less than 1%. Discontinuation for all bleeding-related complaints combined occurred in 26 (1.5%) LNG20 users. Fifty-nine (3.4%) women had a symptomatic ovarian cyst, including 3.2% (32/986) of nulliparous women and 3.7% (27/728) of parous women ($p=.15$). Only 5 (0.3%) participants discontinued LNG20 use because of an ovarian cyst. One death occurred in a LNG20 user due to a pre-existing illness and was considered unrelated to the IUS by the site principal investigator.

Uterine perforation was reported in 3 (0.17%) participants, all among women aged 16–35 years. One perforation occurred with uterine sounding after which placement was not performed. The two (0.11%) perforations that occurred with the IUS required surgical removal, one of which was during treatment for an ectopic pregnancy.

Expulsion was identified in 62 (3.5%) of the 1751 participants enrolled (3.6% of the 1714 with successful placement) and occurred less frequently in nulliparous (20/986, 2.0%) women than parous (41/728, 5.6%) women ($p<.0001$). Most expulsions (80.6%) occurred in the first year of product use with 10 occurring within the first 30 days, 17 within the first 3 months, 30 within the first 6 months, and 50 within the first 12 months. Complete expulsions comprised 27 of the 62 expulsions (43.5%).

Site investigators reported pelvic infection in 10 (0.6%) participants; seven infections were classified as PID and three as endometritis by the site investigator. All 10 infections resolved with outpatient antibiotic treatment. Four pelvic infections were diagnosed within 7 days, one at day 39 and the other five more than 6 months following IUS placement. Among cases classified as PID, two occurred

Table 1
Demographics of study population and contraceptive method at enrollment for women enrolled in a phase 3 study investigating LNG20.

	16–35 years old (n=1600)	36–45 years old (n=151)	Total (n=1751)
Age (years)	26.2 ± 4.4	39.6 ± 2.7	27.3 ± 5.7
Ethnicity			
Hispanic or Latina	237 (14.8)	21 (13.9)	258 (14.7)
Race			
American Indian or Alaska Native	19 (1.2)	2 (1.3)	21 (1.2)
Asian	61 (3.8)	7 (4.6)	68 (3.9)
Black or African American	212 (13.3)	20 (13.2)	232 (13.3)
Native Hawaiian or Other Pacific Islander	5 (0.3)	1 (0.7)	6 (0.3)
White	1250 (78.3)	120 (79.5)	1370 (78.4)
Multiple Races	49 (3.1)	1 (0.7)	50 (2.9)
Body mass index (kg/m ²)*			
25–29.9	390 (24.4)	37 (24.5)	427 (24.4)
≥ 30	383 (24.0)	55 (36.4)	438 (25.1)
≥ 40	79 (4.9)	14 (9.3)	93 (5.3)
Partner status			
Lives with partner	915 (57.2)	106 (70.2)	1021 (58.3)
Nulliparous	989 (61.8)	22 (14.6)	1011 (57.7)
Age (years)	24.8 ± 3.8	38.7 ± 3.0	25.1 ± 4.3
Parous	611 (38.2)	129 (85.4)	740 (42.3)
Age (years)	28.3 ± 4.5	39.8 ± 2.6	30.3 ± 6.1
Contraception at time of enrollment			
Levonorgestrel IUS	111 (6.9)	30 (19.9)	141 (8.1)
Copper IUD	23 (1.4)	7 (4.6)	30 (1.7)
Implant	9 (0.6)	1 (0.7)	10 (0.6)
Combined hormonal contraceptive	623 (38.9)	38 (25.2)	661 (37.7)
Progestin-only oral contraceptive	32 (2.0)	3 (2.0)	35 (2.0)
Barrier method	576 (36.0)	45 (29.8)	621 (35.5)
Other	74 (4.6)	11 (7.3)	85 (4.9)
None	152 (9.5)	16 (10.6)	168 (9.6)

Data presented as n (%) or mean ± standard deviation.

* Data missing for four 16–35 year old participants.

IUS = intrauterine system; IUD = intrauterine device.

in the first 20 days and five occurred after 6 months of use. Nine of the 10 infections occurred during the first year for a 1-year pelvic infection rate of 0.51% (95% CI 0.18, 0.85%). Only three of the 1751 (0.2%) participants had the IUS removed for a pelvic infection (2 PID, 1 endometritis). Chlamydia testing was positive in 23 of 1751 (1.3%) subjects at baseline, none of whom developed pelvic infection.

Of the 661 (38.5%) women who discontinued LNG20 use during the study period, 255 met criteria to be followed for return of spontaneous menses. Almost all had a menses within 2 months (n=241, 94.6%) or 3 months (n=248, 97.3%) following LNG20 discontinuation. Of the 68 women followed for fertility after LNG20 discontinuation, 48 (70.6%) conceived spontaneously within 6 months and 59 (86.8%) within 12 months. The median time to conception was 4 months.

Table 2
Adverse reactions occurring in ≥ 5% of LNG20 users over 3 years [n (%)].

	16–35 years old (n=1600)	36–45 years old (n=151)	Total (n=1751)
Bacterial vaginitis	212 (13.3)	26 (17.2)	238 (13.6)
Vulvovaginal candidiasis	213 (13.3)	20 (13.2)	223 (13.3)
Acne	203 (12.7)	12 (7.9)	215 (12.3)
Headache*	151 (9.4)	21 (13.9)	172 (9.8)
Nausea or vomiting	128 (8.0)	10 (6.6)	138 (7.9)
Dyspareunia	121 (7.6)	2 (1.3)	123 (7.0)
Abdominal discomfort or pain	110 (6.9)	9 (6.0)	119 (6.8)
Breast tenderness or pain	108 (6.8)	10 (6.6)	118 (6.7)
Pelvic discomfort or pain	103 (6.4)	3 (2.0)	106 (6.1)
Depression or depressed mood	86 (5.4)	8 (5.3)	94 (5.4)
Mood changes	84 (5.3)	7 (4.6)	91 (5.2)

* Includes migraine headaches which occurred in 38 (2.4%) women 16–35 years old and 4 (2.6%) women 36–45 years old.

4. Discussion

LNG20 was highly effective at preventing pregnancy consistent with methods the CDC considers the most effective contraceptive options [14]. ACCESS IUS is the first Phase 3 pivotal hormonal IUS trial conducted exclusively in the U.S. The study was designed to demonstrate the efficacy and safety of LNG20 for at least 7 years of intended use. This report captures data for the 3-year indication for use. Data from subsequent planned years of use will be summarized in future reports. Because study participants entered the trial on a rolling basis and all participants have not yet reached the same duration of use, complete year-by-year data on continuation rates and other outcomes are not finalized in this report.

This clinical trial aimed to mirror the demographics of U.S. women likely to use this method of contraception in the U.S., enrolling a broad range of sexually active nulliparous and parous women at public sector, university and private centers. Enrollment in this trial was not restricted by weight/BMI, race or parity and included women from 16 to 45 years of age. The characteristics of women enrolled parallels the 2010 U.S. census with respect to Hispanic ethnicity (16.3% census and 14.7% study), African-American race (12.6%

Table 3
IUS-related* adverse events with incidence ≥ 2% in LNG20 users over 3 years [n (%)].

	16–35 years old (n=1600)	36–45 years old (n=151)	Total (n=1751)
Acne	101 (6.3)	4 (2.7)	105 (6.0)
IUS expulsion	56 (3.5)	6 (4.0)	62 (3.4)
Dyspareunia	48 (3.0)	1 (0.7)	49 (2.8)
Breast tenderness	30 (1.9)	5 (3.3)	35 (2.0)
Dysfunctional uterine bleeding	14 (0.9)	4 (2.7)	18 (1.0)

* Relatedness determined by the principal investigator at the study site.

census and 13.3% study) and Caucasian race (72.4% census and 78.4% study) [15].

This study enrolled a substantial number of nulliparous participants, representing 57.7% of the study efficacy population. This number was not a result of targeted recruitment and thus may represent the interest of nulliparous U.S. women in using highly effective contraceptives such as an IUS. Notwithstanding the number of nulliparous participants, nearly all (98.7%) LNG20 placement attempts were successful.

The most common reason for discontinuation was IUS expulsion, occurring in 3.5% of ACCESS IUS participants. Most expulsions occurred in the first year, consistent with expulsion timing seen with other IUDs [16–18]. A similar expulsion rate (4.2%) was reported in a European study to evaluate the safety and efficacy of LNG20 (under the brand name Levosert™) in women with menorrhagia [19]. Expulsions occurred more frequently in parous participants, which may partly account for the lower overall expulsion rate as this study had relatively fewer parous participants. A recent prospective trial including 5403 U.S. women using an IUD also demonstrated a statistically significantly higher rate of expulsion in parous as compared to nulliparous women (11.4% vs. 8.4%, $p < .001$) over 36 months of follow-up [20].

The 1-year pelvic infection rate in this study of 0.51% is similar to the 0.54% rate reported through 90 days after IUD placement in a group of 57728 women who had IUD placement through a large Northern California Health Maintenance Organization [21]. Unlike results reported among women in populations not screened for STIs [22] we did not find any suggestion of an increased risk of pelvic infection in the first 20 days following insertion.

Ovarian cysts were reported as adverse events in 3.4% of LNG20 participants. This study only collected data on women who were symptomatic as would be appropriate in clinical care of women with an IUS; routine ultrasound surveillance for asymptomatic and clinically non-significant ovarian cysts was not performed. Most ovarian cysts found on routine ultrasound examination in women using hormonal intrauterine contraceptives are asymptomatic and clinically non-significant [23].

Based on the findings of this pivotal Phase 3 study, LNG20 is a highly effective and safe intrauterine contraceptive in a broad range of women for up to 3 years. LNG20 meets the criteria defined by the CDC and the World Health Organization for highly effective contraceptive methods. The LNG20 will address some of the barriers that have previously limited full access to intrauterine contraceptives.

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Appendix A. Supplementary data

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