Levonorgestrel-releasing intrauterine side-by-side comparison

Updated October 2023

Levonorgestrel-releasing intrauterine system side-by-side comparison

	Brand name			
	Kyleena[1]	**Liletta**[2]	**Mirena**[3]	**Skyla**[4]
Manufacturer	Bayer	Allergan/Medicines 360	Bayer	Bayer (Merck
Approval date	2016	2015	2000	2013
FDA-approved indications				
Contraception	Up to 5 y	Up to 8 y	Up to 8 y	Up to 3 y
Treatment of HMB	Na	Up to 5 y in patients who chose IUS as a method of contraception	Up to 5 y in patients who chose IUS as method of contraception	Na
Dosage and administration				
Minimum uterine cavity for insertion (cm)	Pivotal trial did not include parameters. Mean uterine sound depth in pivotal trial (± SD): 7.3 ± 0.9[5]	≥ 5.5	6-10	Pivotal trial did not include parameters. Mean uterine sound depth in pivotal trial (± SD): 7.3 ± 0.9[5]
Insertion	• IUS should be inserted by a trained healthcare provider. • Consult the prescribing information for individual products for information on specific timing of insertion. • In general, if a woman is not currently using hormonal or intrauterine contraception, an IUS can be inserted any time that the provider can be reasonably certain the woman is not pregnant. If inserted during the first 7 d of the menstrual cycle or immediately after a first trimester abortion, back up contraception is not needed. In other instances, a back-up barrier method or abstinence is recommended for 7 d to prevent pregnancy.			
Product characteristics				
LNG reservoir (mg)	19.5	52	52	13.5
LNG release rate				
Initial (mcg/d)	17.5 (at 24 d)	19.5	21 (at 24 d)	14 (at 24 d)
Average release over approved duration (mcg/d)	9	13.5	• 11 (after 5 y) • 7 (after 8 y)	5 (after 3 y)
Frame size (W x H)	28 mm x 30 mm	32 mm x 32 mm	32 mm x 32 mm	28 mm x 30 mm
Inserter	One-handed	One-handed	One-handed	One-handed

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Inserter (diameter)	3.8 mm	4.8 mm[6]	4.4 mm	3.8 mm
Silver ring for improved visibility on ultrasound	Yes	No (IUS is radio-opaque and placement can be verified with ultrasound)	No	Yes
Removal threads	Blue	Blue	Brown	Brown
Latex-free	Yes	Yes	Yes	Yes
Contraindications	• Pregnancy or suspicion of pregnancy. Do not use for emergency contraception. • Congenital or acquired uterine anomaly if it distorts the uterine cavity. • Acute PID or history of PID unless there has been a subsequent intrauterine pregnancy. • Postpartum endometritis or infected abortion in the past 3 mo. • Known or suspected uterine or cervical neoplasia. • Known or suspected breast cancer or other progestin-sensitive cancer. • Uterine bleeding of unknown etiology. • Untreated acute cervicitis or vaginitis or other lower genital tract infections. • Acute liver disease or liver tumor (benign or malignant). • Increased susceptibility to pelvic infection. • A previous IUS that has not been removed. • Hypersensitivity to any component of specific IUS.			
Warnings/precautions	• Remove IUS if pregnancy occurs. If pregnancy occurs, there is increased risk of ectopic pregnancy including loss of fertility, pregnancy loss, septic abortion, and premature labor and delivery. • Group A streptococcal infection has been reported following insertion of LNG IUS. Strict aseptic technique is essential during insertion. • Before using LNG IUS, consider the risks of PID. • Uterine perforation may occur and reduce effectiveness or require surgery. Risk is increased if inserted in women with fixed retroverted uteri, during lactation, and postpartum. • Partial or complete expulsion may occur, which can be unnoticed, leading to loss of contraceptive efficacy. • Evaluate persistent enlarged ovarian follicles or ovarian cysts. • Bleeding patterns may become altered (irregular or amenorrhea). • Can be safely scanned with MRI only under certain conditions (Kyleena and Skyla only).			

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Adverse reactions	(≥ 5% users): Ovarian cysts, vulvovaginitis, abdominal pain/pelvic pain, headache/migraine, acne/seborrhea, dysmenorrhea/uterine spasm, breast pain/breast discomfort, and increased bleeding.	(>10% users): Vaginal bacterial infections, vulvovaginal mycotic infections, acne.	(≥ 10% users): Alterations of menstrual bleeding patterns, abdominal/pelvic pain, amenorrhea, headache/migraine, genital discharge, and vulvovaginitis.	(>10% users): Alterations of menstrual bleeding patterns, vulvovaginitis, abdominal/pelvic pain, acne/seborrhea, headache/migraine, ovarian cyst, and dysmenorrhea/uterine spasm.
Drug interactions	No drug-drug interaction studies have been conducted with hormonal IUS.			
Pharmacology	The local mechanism by which LNG provides contraception has not been conclusively demonstrated. Several mechanisms for pregnancy prevention have been postulated: thickening of the cervical mucus (inhibition of sperm passage through the cervix and inhibition of sperm mobility and function) and alteration of the endometrium.			
Storage	25° C	20-25° C	25° C	25° C
How supplied	1 sterile unit	1 sterile unit	1 sterile unit	1 sterile unit
Efficacy				
Year-by-Year Pearl Index (95% CI)	1 y: 0.16 (0.02, 0.58) 2 y: 0.38 (0.10, 0.96) 3 y: 0.45 (0.12, 1.15) 4 y: 0.15 (0.00, 0.85) 5 y: 0.37 (0.04, 1.33)	1 y: 0.15 (0.02, 0.55) 2 y: 0.37 (0.10, 0.94) 3 y: 0.11 (0.00, 0.62) 4 y: 0.13 (0.00, 0.73) 5 y: 0.16 (0.00, 0.87) 6 y: 0.00 (0.00, 0.69) 7 y: 0.49 (0.06, 1.78) 8 y: 0.00 (0.00, 1.31)	1 y: 0.19 (0.02, 0.70)[7] 5 y: 0.08 (0.02, 0.23)[7] 6 y: 0.34 (0.01, 1.88)[8] 7 y: 0.40 (0.01, 2.25)[8] 8 y: 0.00 (0.00, 1.90)[8] Years 6-8: 0.28 (0.03, 1.00)[8]	1 y: 0.41 (0.31, 0.96) 2 y: 0.30 (0.06, 0.86) 3 y: 0.24 (0.03, 0.88)
Pivotal contraceptive trials – design, baseline characteristics, and results				
Design	Single-blind RCT conducted in 11 countries[5,9]	Open-label trial conducted in US at 29 sites[10-13]	• 3 trials conducted outside of US (AY99,[14] B078,[7] AV97[15]) • Open-label, single arm phase 3 conducted at 54 sites in US (MET study)[8]	Single-blind RCT conducted in 11 countries[5]

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Inclusion	• 18-35 y • Nulliparous and parous	• 16-45 y (efficacy analysis included ≤ 35 y in years 1-6 and ≤ 39 y in years 7 and 8) • Nulliparous and parous • No restriction on body weight	**AY99, B078 studies** • 18-38 y • At least 1 previous pregnancy **AV97 study** • 18-25 y • Nulliparous **MET study** • 18-35 y • Current users of IUS for 4.5 to 5 y (98.3% using for contraception; 1.7% for HMB/contraception)	• 18-35 y • Nulliparous and parous
No. of included women (Full analysis set)	1,452	1,714	• AY99 study (qualified): 1,110 • B078 study: 390 • AV97 study: 94 • MET study: 362	1,432
Baseline characteristics	• Mean age (y): 27.1 (18-35) • Mean BMI (kg/m^2): 25.3 (15.2-57.6) • Nulliparous: 39.5% • IUS/IUD use at baseline: 6.8%	• Mean age (SD) y: 27.3 (5.7) • Mean BMI (kg/m^2): 26.9 ± 6.8 • Nulliparous: 57.7% • IUS/IUD use at baseline: 9.77%	**AY99 study** (qualified) • Mean age (y): 31 (18-38) • Nulliparous: 0.63% • IUD use at baseline: 75% **B078 study** • Mean age (y): 32.5 • IUD use at baseline: 77% **AV97 study** • Mean age (y): 22 **MET study (FAS)** • Mean age (SD) y: 29.4 (3.1) • Nulliparous: 47.2%	• Mean age (y): 27.2 (18-35) • Mean BMI (kg/m^2): 25.3 (15.6-54.9) • Nulliparous: 38.8% • IUS/IUD use at baseline: Not provided

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Successful placement among attempted placements	99.4%	98.7%	• AY99 study: 99% • B078 study: Not reported • AV97 study: 98% • MET study: Na, continuation study	99.6%
Participant evaluation of pain on insertion	• Moderate: 27.4% • Severe: 7.6%	Not reported	**AY99 study** • Moderate: 21% • Severe: 3% **B078 study** – Not reported **AV97 study** • Moderate: 37% • Severe: 21% **MET study**: Na, continuation study	• Moderate: 27.4% • Severe: 7.6%
Safety results				
Discontinuation due to bleeding patterns	• 3 y: 4.9% • 5 y: 5.2%	Over 8 y, 2.6% discontinued due to bleed events. In years 3 to 8, annual rate of discontinuation due to bleeding ranged from 0.1 to 0.5%.	**AY99 study** (qualified) • 5 y: 10.05% **AV97 study** • 1 y: 2% **MET study** • Years 6-8 of use: 3%	4.7%
Amenorrhea	End of 5 y: 22.6%	• Plateaus around 37% to 42% at end of 3 y • End of 7 y and 8 y: 39%	**AY99 study** • End of 5 y: 27% **B078 study** • Not reported **AV97 study** • End of 1 y: 21% **MET study** • 3 y (end of 6 to 8 y: 18.3-33.6% per 90-d reference period)	End of 3 y: 12%
PID	• 3 y: 0.4%	Over 8 y, 0.9% (n = 16) participants diagnosed with PID.	• AY99 study: 0.8% at 5 y	3 y: 0.4%

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	• 5 y: 0.3%	After first y, there were 0 to 2 diagnoses per y	• B078 study: 6.22 per 1000 woman y at 5 y • AV97 study: 0 cases • MET study: 0 cases	
Uterine perforation	5 y: 0.2%	8 y: 0.1% (both occurred during first year)	MET study: 3 y of use (years 6 to 8): 1.1%	3 y: 0%
Pearl Index (95%) for ectopic pregnancy	• 3 y: 0.22 (0.09, 0.45) • 5 y: 0.18 (0.08, 0.36)	• 3 y: 0.12 • 5 y: 0.13	• AY99 study: Not reported • B078 study: 0.38 at 5 y • AV97 study: 0 cases • MET study: 0.14 (0.00-0.77) after 3 y of use (years 6 to 8)	3 y: 0.10 (0.02, 0.29)
Return to fertility	169 women evaluated • 3 mo: 37.4% conceived • 12 mo: 71.2% conceived	165 women discontinued IUS within 60 mo of use[16] • At 12 mo, 142 (86.1%) conceived • Median time to conception: 92 d	• 138 women evaluated at 12 mos, 92% conceived[17] • In MET study, 12-mo return to fertility rate was 77.4%[8]	Not reported in studies

Evidence Summary

In a 2017 Practice Bulletin, The American College of Obstetricians and Gynecologists recommend that IUDs, including LNG-releasing IUSs be offered routinely as safe and effective contraceptive options for most women including nulliparous women and adolescents.[18] In the US there are currently 4 FDA-approved LNG-releasing IUSs: Mirena (approval year: 2000),[3] Skyla (2013),[4] Liletta (2015),[2] and Kyleena (2016).[1] While a copper IUD (Paragard) is also available in the US, this evidence summary is limited to LNG-releasing IUSs. All of the LNG-IUSs are T-shaped and include a polydimethylsiloxane sleeve that contains a LNG reservoir, which is released over the approved duration of use.[1-4] Liletta and Mirena have a LNG content of 52 mg [2,3] while Skyla and Kyleena have a reduced total levonorgestrel content of 13.5 mg[4] and 19.5 mg,[1] respectively. The initial and average LNG release rates are different among the approved systems. Other potential differentiators are the smaller T-frame size and inserter diameter of Skyla and Kyleena.[1,4]

All of the LNG-IUSs are approved for intrauterine contraception in nulliparous and parous women and share a common mechanism of action.[18] At present, approved durations of use vary among the systems: Mirena and Liletta are approved for 8 years of use[2,3] and Kyleena and Skyla are approved for shorter durations of use of 5 and 3 years, respectively.[1,4] Intrauterine devices are considered one of the most effective reversible contraceptive methods. All the currently approved LNG-releasing IUSs have a Pearl Index of less than 1 over their approved duration, which corresponds to a failure rate of less than 1 pregnancy per 100 woman-years of exposure (eg, 100 women over 1 year of use). Results from pivotal IUS trials are summarized in the comparative table. Data on comparative effectiveness for contraception is limited to a single phase 2 trial that compared Skyla and Kyleena with Mirena.[19] The sample size of the trial was too small to evaluate noninferiority; however, the CIs of the unadjusted 3-year Pearl Indexes for Skyla, Kyleena, and Mirena overlapped: 0.17 (95% CIs, 0-0.93), 0.82 (95% CI, 0.27-1.92), and 0 (95% CI, 0-0.59), respectively.[19] Due to the high effectiveness of IUSs, it is unlikely a comparative trial will have a large enough sample size to assess superiority. Therefore, contraceptive effectiveness is not a differentiator.

Results of multiple studies suggest that IUS placement in nulliparous women is more painful and more difficult than placement in parous women.[20] Because of their smaller T-frame bodies and inserter diameters, Skyla and Kyleena are marketed as options to reduce insertion pain and improve ease of insertion in women that have a narrower cervical canal or a smaller uterine cavity. Ease of insertion and pain on insertion were included as endpoints in phase 2 and 3 trials that evaluated Skyla and Kyleena.[5,19] In these trials, investigators rated ease of insertion as easy, slightly difficult, or very difficult and women rated pain on insertion as none, mild, moderate, or severe. In the trials, investigators were aware of the system that was inserted. In the phase 2 trial with Mirena as an active comparator, 21.5% of included women were nulliparous. Investigators more frequently rated placement as easy with Skyla or Kyleena compared with Mirena (94% vs. 86.2%, respectively; $P < .001$) and more women reported either no pain or mild pain with Skyla or Kyleena (72.3%) insertion compared with Mirena (57.9%) insertion.[19] Of note, the diameter of the commercially available inserter for Mirena is 4.4 mm, but the inserter used in the trial had a diameter of 4.75 mm. The clinical significance of the difference in inserter diameter is unknown. In the noncomparative phase 3 trial, 39.2% of participants were nulliparous (Kyleena: 39.5%; Skyla: 38.8%).[5] In the subgroup of nulliparous women, 48.6% and 14.5% were administered analgesia and local anesthesia before the procedure, respectively. In nulliparous women, 95% of placements of Skyla and Kyleena were successful at first attempt and investigators rated placement as easy in 84.2% (compared with 94.5% in women with a previous vaginal delivery). Only 42% of nulliparous women reported either no pain or mild pain with Skyla or Kyleena insertion (compared with 81.9% of women with a previous vaginal delivery).[21] In a phase 3 study that enrolled adolescent nulliparous women (mean age: 16.2 years, range: 12-18 years), 94.4% of investigators rated placement of Skyla as easy and 54.8% of adolescents reported either no pain or mild pain at placement.[22]

The disparity in reported ease and pain of Skyla insertion between phase 3 studies may be attributable to differences in use of adjunctive drugs. In the adolescent study, 31.9% of participants received paracervical/intracervical local anesthesia (compared with 14.5% of women aged 18 to 35 years), dilation was performed in 29.3% of participants, and 4.3% were administered misoprostol as a cervical softner.[21,22] While results of a systematic review of the literature suggest that local anesthetics may mitigate the pain on insertion,[23] results from an exploratory post-hoc analysis of 3 trials of Skyla suggest a positive association between pain and analgesic administration ($P = .0262$) with women generally reporting less pain without prophylactic analgesia administration.[6]

Results from the phase 2 trial[19] that evaluated parous and nulliparous women collectively differ notably from results of the phase 3 trial[21] that analyzed parous and nulliparous subgroups separately, suggesting that a smaller inserter and T-frame do not completely mitigate the pain or difficulty associated with insertion of an IUS in nulliparous women. Additionally, without use of a validated pain scale, it is difficult to determine the clinical meaningfulness of reductions in pain reported in currently published trials with the smaller IUSs. The pain associated with insertion of Liletta was not evaluated in its phase 3 trial; however, over half of the participants in the trial were nulliparous (57.7%) and insertion was successful in 98.7% of the study population (parous and nulliparous).[14] Recent data demonstrate that high levels of anticipated pain correlates with high levels of actual pain during insertion, suggesting that many factors contribute to the pain experience during IUS insertion and that a smaller inserter and T-frame cannot completely mitigate pain on insertion.[24]

All IUSs may cause progestin-related adverse events such as headaches, nausea, breast tenderness, and mood changes. More serious adverse events that include ectopic pregnancy, uterine perforation, PID, and ovarian cysts may also occur with all IUSs. With a smaller initial reservoir of LNG, the average release of LNG per day over the approved duration is smaller with Skyla (6 mcg) and Kyleena (9 mcg) compared with Liletta and Mirena.[1-4] Whether or not this is associated with a reduction in progestin-related adverse effects is unknown. In the phase 2 comparative trial, there were no differences in the rate of progestin-related adverse events among Skyla, Kyleena, and Mirena, but the trial was not powered to detect differences in adverse events.[19] The rate of ectopic pregnancies is low with all the IUSs. In pivotal trials, the calculated Pearl Indexes (number of ectopic pregnancies per 100 woman-years of exposure) were 0.18 with Kyleena at 5 years,[9] 0.13 with Liletta at 5 years,[12] 0.14 with Mirena at 8 years,[8] and 0.10 with Skyla at 3 years.[5] Although not based on head-to-head data, the risk for an ectopic pregnancy is generally assumed to be similar among IUSs. Likewise the incidence of uterine perforation or PIDs is low and generally consistent across the class with less than 1% of women experiencing a perforation or PID in pivotal trials of Kyleena, Liletta, Mirena, and Skyla.[1-4,18] Significantly more ovarian cysts were reported with Mirena (22%) than with Skyla (5.6%) or Kyleena (8.6%) over 3 years of use[19]; however, the study reported both asymptomatic and symptomatic cysts detected on routine ultrasounds. Therefore, it is unknown if Mirena is associated with an increased incidence of

symptomatic ovarian cysts. In the pivotal Liletta trial, only symptomatic ovarian cysts were reported. The incidence of symptomatic cysts with Liletta over 3 years and 5 years of use was 3.4%[10] and 4.5%[2] respectively, suggesting that asymptomatic cysts likely made up most of the excess cysts with Mirena. This observation is supported by additional trial data.[25] Due to the local impact of LNG on the endometrium, most users of IUSs experience a reduction in menstrual bleeding. IUSs with the highest content of LNG (Liletta and Mirena) appear to be associated with the highest incidence of amenorrhea over the approved duration of use (Skyla: 12% at 3 years; Kyleena: 22.6% at 5 years; Liletta: plateau of 37% to 42% at end of 3 years); however, rates of discontinuation due to abnormal bleeding patterns/amenorrhea are low and similar among the IUSs.

Because IUSs cause endometrial atrophy, they are effective for the treatment of HMB. Mirena and Liletta are FDA approved for the treatment of HMB in women who choose IUSs as a method of contraception.[2,3] In pivotal trials, Liletta and Mirena significantly reduced MBL from baseline and were associated with high rates of women achieving treatment success, defined as MBL <80 mL and a 50% reduction in MBL from baseline during 6 cycles of treatment.[26,27] In its pivotal trial, Liletta was associated with a higher than expected rate of device expulsion; however, a potential explanation is that the baseline BMI was higher in the Liletta phase 3 trial vs. other US-based trials and almost all expulsions occurred in obese, parous participants.[26] Results from 2 head-to-head comparisons suggest that Liletta is equivalent or noninferior to Mirena for reduction in MBL and for percentage of women achieving treatment success (refer to Appendix 1 for summary of HMB trial results).[28,29]

The recommended use of Mirena was previously limited to women who had at least 1 child, but after removal of this stipulation in 2017, all the IUSs are approved for contraception in nulliparous women. As a result, an important consideration is the return of fertility after cessation of use. In several trials, a subset of women desiring pregnancy after IUS removal were evaluated. Conception was achieved in 71.2%, 86.1%, and 77.4 to 92% within 12 months of removal of Kyleena, Liletta, and Mirena, respectively.[8,9,16,17]

In summary, there are 4 LNG-IUSs approved for intrauterine contraception in nulliparous and parous women: Mirena, Skyla, Liletta, and Kyleena. Mirena and Liletta are approved for up to 8 years and Kyleena and Skyla are approved for up to 5 years and 3 years, respectively. Mirena and Liletta are additionally approved for the treatment of HMB for up to 5 years. In general, IUSs are highly effective for the prevention of pregnancy over their approved duration of use and there are likely no differences in efficacy among IUSs. Skyla and Kyleena are marketed as options to reduce insertion pain and improve ease of insertion in nulliparous women due to their smaller T-frame bodies and inserter diameters. Results of studies have shown that Skyla and Kyleena may be associated with a decreased incidence of insertion pain compared with Mirena, but overall do not mitigate moderate to severe insertion pain for 40 to 60% of nulliparous women. Selection between IUSs of different approved durations will depend on an individual patient's contraception needs. For those that desire a shorter duration of intrauterine contraception, Skyla offers the shortest duration followed by Kyleena. For those desiring a longer duration of intrauterine contraception, Mirena and Liletta are approved for up to 8 years of use. In addition to having a smaller T-frame body and inserter diameter, Kyleena has a lower average daily LNG release rate over its approved duration compared with Mirena and Liletta. A lower LNG reservoir and daily release rate appears to be associated with a lower incidence of amenorrhea and may be associated with a lower incidence of asymptomatic ovarian cysts. Mirena and Liletta have the same LNG reservoir and similar initial and daily LNG release rates. Although Mirena and Liletta have not been compared head-to-head for the prevention of pregnancy, results from head-to-head studies suggest Liletta and Mirena are similarly effective for the treatment of HMB. The selection among IUSs will likely be based on patient and financial considerations.

Abbreviations: BMI = body mass index; CI = confidence intervals; FAS = full analysis set; H = height; HMB = heavy menstrual bleeding; IUD = intrauterine device; IUS = intrauterine system; LNG = levonorgestrel; MBL = menstrual blood loss; MRI = magnetic resonance imaging; PID = pelvic inflammatory disease; RCT = randomized, controlled trial; SD = standard deviation; W = width

References

1. Kyleena [package insert]. Whippany, NJ: Bayer; 2023.
2. Liletta [package insert]. Irvine, CA: Allergan; 2023.
3. Mirena [package insert]. Whippany, NJ: Bayer; 2022.
4. Skyla [package insert]. Whippany, NJ: Bayer; 2023.

5. Nelson A, Apter D, Hauck B, et al. Two low-dose levonorgestrel intrauterine contraceptive systems: a randomized controlled trial. *Obstet Gynecol*. 2013;122(6):1205-1213.
6. Gemzell-Danielsson K, Apter D, Lukkari-Lax E, Roth K, Serrani M. Overcoming barriers to levonorgestrel-releasing intrauterine system placement: an evaluation of placement of LNG-IUS 8 using the modified EvoInserter in a majority nulliparous population. Contraception. 2017;96(6):426-431.
7. Center for Drug Evaluation and Research. Application Number: 21-225. Medical Review. US Food and Drug Administration website. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2000/21-225.pdf_Mirena_Medr.pdf. Published February 2, 2000. Accessed February 21, 2019.
8. Jensen JT, Lukkari-Lax E, Schulze A, Wahdan Y, Serrani M, Kroll R. Contraceptive efficacy and safety of the 52-mg levonorgestrel intrauterine system for up to 8 years: findings from the Mirena Extension Trial. *Am J Obstet Gynecol*. 2022;227(6):873.e1-873.e12.
9. Gemzell-Danielsson K, Apter D, Dermout S, et al. Evaluation of a new, low-dose levonorgestrel intrauterine contraceptive system over 5 years of use. *Eur J Obstet Gynecol Reprod Biol*. 2017;210:22-28.
10. Eisenberg DL, Schreiber CA, Turok DK, Teal SB, Westhoff CE, Creinin MD for ACCESS IUS Investigators. Three-year efficacy and safety of a new 52-mg levonorgestrel-releasing intrauterine system. *Contraception*. 2015;92(1):10-16.
11. Thomas M, Chen B, Keder L, Kimble T, Jensen J, Creinin M. Four-year efficacy and safety of the Liletta levonorgestrel intrauterine system. *Obstet Gynecol*. 2017;129(5):11S-12S.
12. Teal SB, Turok DK, Chen BA, Kimble T, Olariu AI, Creinin MD. Five-year contraceptive efficacy and safety of a levonorgestrel 52-mg intrauterine system. *Obstet Gynecol*. 2019;133(1):63-70.
13. Creinin MD, Schreiber CA, Turok DK, Cwiak C, Chen BA, Olariu AI. Levonorgestrel 52 mg intrauterine system efficacy and safety through 8 years of use. *Am J Obstet Gynecol.* 2022;227(6):871.e1-871.e7.
14. Lukkainen T, Allonen H, Haukkamaa M. Effective contraception with the levonorgestrel-releasing intrauterine device: 12-month report of a European multicenter study. *Contraception*. 1987;36(2):169-179.
15. Suhonen S, Haukkamaa M, Jakobsson T, Rauramo I. Clinical performance of a levonorgestrel-releasing intrauterine system and oral contraceptive in young nulliparous women: a comparative study. *Contraception*. 2004;69(5):407-412.
16. Carr BR, Thomas MA, Gangestad A, Eisenberg DL, Olariu A, Creinin MD. Conception rates in women desiring pregnancy after levonorgestrel 52 mg intrauterine system (Liletta) discontinuation. *Contraception*. 2021;103(1):26-31.
17. Andersson K, Batar I, Rybo G. Return to fertility after removal of a levonorgestrel-releasing intrauterine device and Nova-T. *Contraception*. 1992;46(6):575-584.
18. Committee on Practice Bulletins – Gynecology and the Long-Acting Reversible Contraception Work Group. *Obstet Gynecol*. 2017;130(5):e251-e269.
19. Gemzell-Danielsson K, Schellschmidt I, Apter D. A randomized, phase II study describing the efficacy, bleeding profile, and safety of two low-dose levonorgestrel-releasing intrauterine contraceptive systems and Mirena. *Fertil Steril.* 2012;97(3):616-622.e1-3.
20. Lohr PA, Lyus R, Prager S. Use of intrauterine devices in nulliparous women. *Contraception*. 2017;95(6):529-537.
21. Gemzell-Danielsson K, Apter D, Hauck B, et al. The effect of age, parity and body mass index on the efficacy, safety, placement and user satisfaction associated with two low-dose levonorgestrel intrauterine contraceptive systems: Subgroup analyses of date from a phase III trial. *PLoS One*. 2015;10(9):e0135309.
22. Gemzell-Danielsson K, Buhling KJ, Dermout SM, Lukkari-Lax E, Montegriffo E, Apter D. A phase III, single-arm study of LNG-IUS 8, a low-dose levonorgestrel intrauterine contraceptive system (total content 13.5 mg) in postmenarcheal adolescents. *Contraception*. 2016;93(6):507-512.
23. Lopez LM, Bernholc A, Zeng Y, et al. Interventions for pain with intrauterine device insertion. *Cochrane Database Syst Rev*. 2015;7:CD007373.
24. Dina B, Peipert LJ, Zhao Q, Peipert JF. Anticipated pain as a predictor of discomfort with intrauterine device placement. *Am J Obstet Gynecol.* 2018;218(2):236.e1-236.e9.
25. Inki P, Hurskainen R, Palo P, et a. Comparison of ovarian cyst formation in women using the levonorgestrel-releasing intrauterine system vs. hysterectomy. *Ultrasound Obstet Gynecol*. 2002;20(4):381-385.
26. Creinin MD, Barnhart KT, Gawron LM, Eisenberg D, Mabey RG Jr, Jensen JT. Heavy menstrual bleeding treatment with a levonorgestrel 52-mg intrauterine device. *Obstet Gynecol*. 2023;141(5):971-978.
27. Kaunitz AM, Bissonnette F, Monteiro I, Lukkari-Lax E, Muysers C, Jensen JT. Levonorgestrel-releasing intrauterine system or medroxyprogesterone for heavy menstrual bleeding: a randomized controlled trial. *Obstet Gynecol*. 2010;116(3):625-632.
28. Mawet M, Nollevaux F, Nizet D, et al. Impact of a new levonorgestrel intrauterine system, Levosert(®), on heavy menstrual bleeding: results of a one-year randomized controlled trial. *Eur J Contracept Reprod Health Care*. 2014;19(3):169-179.

29. Ilyin AB, Khasanov AA, Suturina LV, et al. Comparison of two levonorgestrel-releasing intrauterine systems for the treatment of heavy menstrual bleeding: a randomized, controlled, phase 3 trial. *Eur J Contracept Reprod Health Care*. 2021;26(6):491-498.

Appendix 1: Pivotal and comparative trials in HMB

Study reference/ study design	N	Patient Selection	Treatment Intervention	Significant outcomes		
				Summary results	Endpoints and results	Safety
Obstet Gynecol. 2010;116:625-632. MC, OL, RCT	165	**Inclusion:** Parous women ≥ 18 y with heavy bleeding (MBL ≥ 80 mL/cycle) **Major exclusion criteria**: • Changes in menstrual regularity, hot flushes, sleeping disorders, or changes in mood within 3 mo preceding study • Breast feeding • Congenital or acquired uterine abnormality • History of organic causes of abnormal uterine bleeding • BMI ≥ 35 kg/m^2 **Baseline characteristics** • Mean age y (SD): Mirena: 38.3 (5.2); MPA: 39.3 (5.4) • Mean BMI, kg/m^2 (SD): Mirena: 27.2 (3.4); MPA: 27.4 (4.6)	**Treatment groups** • Mirena • Oral MPA 10 mg once daily for 10 consecutive d in each cycle, starting on day 16 of menstrual cycle	Mirena >> MPA for all outcomes	**ITT population** (n = 165) **Primary outcome** (based on alkaline hematin testing) Absolute change in MBL from baseline to end of study • Mirena: -128.8 mL • MPA: -17.8 mL (*P* <.001) **Secondary outcomes** Successful treatment: MBL <80 mL and 50% reduction in MBL from baseline • Mirena: 67/79 (84.8%) • MPA: 18/81 (22.2%) (*P*<.001)	**Discontinuation due to AEs** • Mirena: n =4 • MPA: n =2 **Expulsions** 2 complete; 2 partial
Obstet Gynecol. 2023;141:971-978. MC, OL, single arm, phase 3 trial	105	**Inclusion**: Nulliparous and parous women aged 18-50 y who reported regular heavy menses (MBL ≥ 80 mL/cycle) **Major exclusion criteria**: Structural, infectious, medical, drug, premalignant or malignant causes of HMB **Baseline characteristics** (enrolled population, n = 105) • Mean age y (SD): 35.4 (8.3)	**Treatment group** • Liletta Participating women were followed for 6 mo.	Non-comparative	Subjects who provided bleeding outcomes at cycle 3 or 6 (n = 89) **Primary outcome** (based on alkaline hematin testing) Successful treatment: MBL <80 mL and 50% reduction in MBL from baseline • Subjects with any follow-up: 81/89 (91%; 95% CI, 85.1-97%)	**Discontinuation due to AEs** 7 (bleeding, uterine pain, uterine cramping, mood changes) **Expulsions** 8 complete; 1 partial (8.6%)

Study reference/ study design	N	Patient Selection	Treatment Intervention	Summary results	Significant outcomes	
					Endpoints and results	Safety
		• Mean BMI, kg/m^2 (SD): 31.1 (9) • Baseline MBL mL (SD): 165 mL (79)			• All enrolled subjects: 77.1% (95% CI, 69.1-85.2%) **Secondary outcomes** Percentage decrease in blood loss in subject with any follow-up • Cycle 3: 93.3% (86.1-97.7%) • Cycle 6: 97.6% (90.4-100%)	
Eur J Contracept Reprod Health Care. 2014;19(3):169-179. MC, SB, RCT (Equivalency study)	280	**Inclusion**: Women aged ≥ 18 y who had a clinical diagnosis of HMB at least 6 mos prior to screening **Major exclusion criteria**: Pregnancy; history of endometrial ablation or curettage during preceding 3 mo; structural, infectious, or malignant causes of HMB; BMI ≥ 30 kg/m^2 **Baseline characteristics** (ITT population) • Mean age y (SD): Liletta: 37.9 (6.2); Mirena: 37.7 (6.1) • Mean BMI, kg/m^2 (SD): Liletta: 23.5 (3); Mirena: 23.9 (3) • Mean MBL mL (SD): Liletta: 180.6 (81.9); Mirena: 187.7 (103.4)	**Treatment groups** • Liletta (n = 142) • Mirena (n = 138) Both IUSs were inserted within first 7 d of menstrual cycle. Participating women were followed for 12 mos.	Liletta = Mirena	Equivalency evaluated in ITT population (n = 280). Equivalency margin defined a priori as ± 20 mL **Primary outcome** (based on modified Wyatt pictogram) Absolute change in MBL from baseline to end of study (12 mo) • Liletta: -142.3 mL • Mirena: -146.4 mL; Difference: -4.1 mL (95% CI, -13.5-5.4; *P* = .3972) **Secondary outcomes** Increase in ferritin (mcg/L) level • Liletta: 16 • Mirena: 15.5 (*P* = .8203) Increase in Hgb (g/dL) level • Liletta: 0.9 • Mirena: 0.9 (*P* = .8668) Endometrial thickness (mm) • Liletta: -7.3 • Mirena: -6.9 (*P* = .2282)	**Discontinuation due to AEs** • Liletta: n = 7 • Mirena: n = 8 **Ovarian cysts** • Liletta: 10% • Mirena: 15.2% **Expulsions** • Liletta: n = 6 • Mirena: n = 5

Study reference/ study design	N	Patient Selection	Treatment Intervention	Significant outcomes		
				Summary results	Endpoints and results	Safety
Eur J Contracept Reprod Health Care. 2021;26(6):491-498. MC, SB, RCT (Noninferiority study)	312	**Inclusion:** Women aged 18-45 y who had clinical symptoms of HMB for ≥ 6 mo, defined as ≥ 80 mL blood loss determined by a modified Wyatt pictogram. **Major exclusion criteria**: Structural or non-structural etiologies of HMB; use of hormonal or drug treatment for HMB within previous 3 mos. **Baseline characteristics (modified ITT population)** • Mean age y (SD): Liletta: 37.2 (5.8); Mirena: 37.0 (5.9) • Mean BMI, kg/m^2 (SD): Liletta: 24.1 (3.1); Mirena: 23.9 (3.2) • Mean MBL mL (SD): Liletta: 163.1 (71.7); Mirena: 159.8 (66.9)	**Treatment groups**: • Liletta (n = 158) • Mirena (n = 154) Both IUSs were inserted within first 7 d of menstrual cycle. Participating women were followed for 6 mos.	Liletta noninferior to Mirena for absolute change in MBL	Noninferiority evaluated at a NIM of ≤ 0.75 in the per-protocol population (n = 300) ***Primary outcome*** (based on modified Wyatt pictogram) Absolute change in MBL from baseline to end of study (6 mo) • Liletta: -130 mL • Mirena: -127 mL Liletta/Mirena ratio: 1.025 (95% CI, 0.919-1.130) ***Secondary outcomes*** Successful treatment: MBL <80 mL and 50% reduction in MBL from baseline • Liletta: 139/154 (90.3%; 95% CI, 0.84-0.94) • Mirena: 126/146 (86.3%; 95% CI, 0.80-0.92) Mean (SD) absolute change from baseline to 6 mo in Hgb (g/L) • Liletta: 4.7 (13.1) • Mirena: 6.2 (11.5) *P* = .8627 Mean (SD) absolute change from baseline to 6 mo in ferritin (mcg/L) • Liletta: 9.7 (29) • Mirena: 15.2 (32.5) *P* = .7152	Expulsions • Liletta: n = 2 • Mirena: None No significant differences between groups for the following common AEs: intermenstrual bleeding, frequent bleeding, amenorrhea, weight increased, breast pain, menstruation delayed, vaginal hemorrhage, and dysmenorrhea.

Abbreviations: AEs = adverse events; BMI = body mass index; ITT = intent to treat; IUS = intrauterine system; Hgb = hemoglobin; HMB = heavy menstrual bleeding; MBL = menstrual blood loss; MC = multi-center; MPA = medroxyprogesterone; NIM = noninferiority margin; OL = open label; RCT = randomized, controlled trial; SB = single blind; SD = standard deviation;

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