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Levonorgestrel 52-mg Intrauterine Device Efficacy and Safety After More Than 8 Years of Use

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The levonorgestrel 52-mg intrauterine device (IUD) is approved for contraception for 8 years. We evaluated outcomes for 339 phase 3 study participants aged 16–35

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Each author has confirmed compliance with the journal's requirements for authorship.

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Beatrice A. Chen has served on the Advisory Board for Merck & Co. Her university department receives contraceptive research funding for Dr. Chen from Medicines360, Mylan, and Sebela. Thomas Kimble has served on the Advisory Board for Merck & Co. His university department receives contraceptive research funding for Dr. Kimble from Bayer HealthCare, Chemo Research SL, Medicines360, Organon, and Sebela. Lisa H. Harris' university department formerly received contraceptive research funding for her from Medicines360, Bayer and Organon. Jennifer L. Kerns' university department formerly received contraceptive research funding for her from Medicines360. Andrea I. Olariu is an employee of Medicines360. Mitchell D. Creinin has received speaking honoraria from Gedeon Richter, Mayne and Organon. He has served on the Advisory Boards for Evofem, Fuji Pharma, Gedeon Richter, GlaxoSmithKline, Mayne, Merck & Co., OLIC, Organon, and Searchlight. He has been a Consultant for Estetra SRL, Libbs, Mayne, and Medicines360, and his university department receives contraceptive research funding for Dr. Creinin from Chemo Research SL, Evofem, HRA Pharma, Medicines360 (includes support for medical and safety oversight of this study), Merck & Co., and Sebela.

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years at enrollment who used the IUD for more than 8 years. At study closure, 83 and 77 participants reached 9 and 10 years, respectively. No pregnancies occurred during years 9 and 10. Expulsion occurred in one (0.3%) participant, a partial expulsion during year 10. No perforations, pelvic infections, or IUD-related serious adverse events were noted. Absence of bleeding or spotting was reported by 33 (39.8%) and 28 (36.4%) participants at years 9 and 10, respectively. The levonorgestrel 52-mg IUD demonstrates continued efficacy and safety in a small population of users during years 9 and 10 of use.

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The levonorgestrel 52-mg intrauterine device (IUD) is approved by the U.S. Food and Drug Administration for contraception for 8 years.^{1,2} Approximately 99% of levonorgestrel 52-mg IUD users will not become pregnant with up to 8 years of continuous use.¹ The ACCESS IUS (A Contraceptive Clinical Efficacy and Safety Study of an IUS) phase 3 trial evaluated Liletta for up to 10 years of use for contraception. After an adequate number of participants for regulatory submission reached 8 years of use in 2021, the study closed because it was unlikely the study would have enough participants reach 9 or 10 years for additional regulatory approvals. Here we report pregnancy rates, safety, and absence of bleeding or spotting outcomes in participants who used the IUD for more than 8 years.



Table 1. Demographics of the Study Population at Enrollment and Entering Year 9 for Participants in a Phase 3 Study Who Had Successful Placement of a Levonorgestrel 52-mg Intrauterine Device

Characteristic	Entering Study (N=1,714)	Entering Year 9 (n=339)
Age (y)	27.3±5.7	35.3±6.2
35 or younger	1,568 (91.5)	181 (53.4)
36–39	85 (5.0)	73 (21.5)
40 or older	61 (3.6)	85 (25.1)
Race		
Asian	67 (3.9)	16 (4.7)
Black	225 (13.1)	35 (10.3)
White	1,342 (78.3)	279 (82.3)
None of the above	76 (4.4)	9 (2.7)
Missing	4 (0.2)	0
Ethnicity		
Hispanic or Latina	251 (14.6)	37 (10.9)
BMI (kg/m ²)*	26.9±6.8	27.3±7.3
30.0 or higher	433 (25.3)	88 (26.0)
Parity		
Nulliparous	986 (57.5)	191 (56.3)
Marital status		
Never married	1,081 (63.1)	215 (63.4)
Married or ever married	533 (36.9)	124 (36.6)

BMI, body mass index.

Data are mean±SD or n (%).

* Data missing for four participants at study entry.

METHODS

The ACCESS IUS trial started in December 2009 and followed 1,568 participants aged 16–35 years at enrollment for up to 10 years and 146 participants aged 36–45 years at enrollment for up to 8 years. The study was approved by a central (Advarra) or local IRB for each center, as applicable. Study entry criteria and methodology have been published previously.^{1,3,4} At the initial screening visit, demographic information was obtained, which included race (per U.S. Census standard criteria) as required for regulatory approval studies. During study years 9 and 10, participants attended study visits every 6 months, undergoing urine pregnancy testing and an examination to confirm IUD presence. Efficacy evaluations were planned to include all participants as well as only those younger than age 40 years at the end of the use year, based on current U.S. Food and Drug Administration guidance. Cycles were excluded if other contraception was used. Safety evaluations were based on adverse-event reporting, with investigators assessing study drug relationship to the event. The study pro-

ocol defined *pelvic infection* as clinical diagnosis of endometritis or pelvic inflammatory disease by a study or nonstudy practitioner. *Partial expulsion* was defined as the IUD stem visible in cervical os on examination or increased bleeding or cramping symptoms with the IUD in the lower uterus or cervix by ultrasonography. *Absence of bleeding or spotting* was defined as no flow for the preceding 90 days.

RESULTS

Three hundred thirty-nine participants used the IUD for more than 8 years (254 [74.9%] younger than age 40 years), including 166 for more than 8.5 years. Characteristics of participants at study entry and those using the IUD for more than 8 years are presented in Table 1. At study closure, 83 and 77 participants completed 9 and 10 years of use, respectively, with 64 (77.1%) and 44 (57.1%), respectively, younger than age 40 years. Annual cycles of exposure were 2,062 and 966 in the 9th and 10th years, respectively. No pregnancies occurred during years 9 and 10. Expulsion occurred in one (0.3%) participant during years 9 and 10, a partial expulsion at 9 years and 19 days of use. No perforations, pelvic infections, or IUD-related serious adverse events were noted during years 9 and 10. Absence of bleeding or spotting was reported by 33 (39.8%) and 28 (36.4%) participants at years 9 and 10, respectively. No participants discontinued for bleeding symptoms during the 2-year time period.

DISCUSSION

These data support the efficacy and safety of the levonorgestrel 52-mg IUD during the 9th and 10th years of continuous use. The demographics for participants who entered the 9th year were similar to the demographics at study entry, other than age; of note, 56% of participants were nulliparous, showing that individuals without children desire methods that provide long-term contraception. The rates of absence of bleeding or spotting remained approximately 40% in years 9 and 10, a rate similar to that reported for years 3 through 8.¹

The in vivo levonorgestrel-release rates for this IUD at the end of 7 and 8 years are 7.5 micrograms/day and 6.5 micrograms/day, respectively.⁵ For comparison, the levonorgestrel 13.5-mg IUD, which is approved for 3 continuous years of use, has an in vivo levonorgestrel-release rate of 5 micrograms/day at the end of 3 years.⁶ Accordingly, we would expect the levonorgestrel 52-mg IUD to continue to demonstrate clinical efficacy after more than 8 years.

The limited data we present are insufficient to confirm contraceptive efficacy of the levonorgestrel



52-mg IUD after more than 8 years of continuous use but may provide relevant data in situations in which a patient has not had the IUD removed before that time.

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Authors' Data Sharing Statement

Will individual participant data be available (including data dictionaries)? *No*.

What data in particular will be shared? *Not available*.

What other documents will be available? *Not available*.

When will data be available (start and end dates)? *Not applicable*.

By what access criteria will data be shared (including with whom, for what types of analyses, and by what mechanism)? *Not applicable*.

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