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Brief Research Article

Six-Year Contraceptive Efficacy and Continued Safety of a Levonorgestrel 52mg Intrauterine System

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22 Presented in part as a poster abstract at the 2019 American College of

23 Obstetrics and Gynecology Annual Clinical Meeting

24 **Conflicts of Interest:** Carolyn L. Westhoff has served on Data Safety

25 Monitoring Boards for studies sponsored by Bayer and Merck & Co, on an

26 Advisory Board for Agile Therapeutics, and has been a consultant for Mithra.

27 Her university department receives contraceptive research funding from

28 Sebela, and Medicines360. Lisa M. Keder has served as a consultant for

29 Bayer and trainer for Merck & Co. Her university department receives

30 contraceptive research funding from Bayer, Medicines360, and Sebela.

31 Angelina Gangestad has served on an advisory board for Bayer Healthcare.

32 Her university department receives contraceptive research funding from

33 Agile, Bayer Healthcare, Femasys and Medicines360. Stephanie B. Teal has

34 served on a Data Safety and Monitoring Board for Merck & Co. Her university

35 department receives contraceptive research funding from Bayer HealthCare,

36 Medicines360, Merck & Co., and Sebela. Andrea I. Olariu is a Medicines360

37 employee. Mitchell D. Creinin has served on Advisory Boards for Lupin and

38 Merck & Co. He has been a consultant for Danco, Estetra, Exeltis and

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41 Co., and Sebela.

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43**Clinical Trial Registration:** Clinicaltrials.gov, NCT00995150

44**Word counts:** Abstract: 97

45 Implications: 23

46 Manuscript (lines 58-146): 1104

47**Tables:** 2

Abstract

48**Objective:** To assess 6-year contraceptive efficacy and safety of a
49levonorgestrel 52mg intrauterine system (IUS).

50**Study Design:** We assessed pregnancy rates through 72 months in women
51aged 16-35 years at enrollment and safety in all participants (aged 16-45
52years, n=1751) in an ongoing 10-year phase-3 trial.

53**Results:** Over six years, nine pregnancies occurred (none in year 6) for a
54life-table pregnancy rate of 0.87 (95% CI .44-1.70). Adverse event rates
55remain low through 6 or more years of use. Two expulsions occurred in year
566.

57**Conclusion:** This levonorgestrel 52mg IUS is a highly effective and safe
58contraceptive over 6 years of use.

Implications: The levonorgestrel 52mg IUS shows high 6-year
contraceptive efficacy and a low rate of adverse events through 6 or more
years of use.

59**Keywords:** levonorgestrel, intrauterine system, Liletta, efficacy, safety

601.0 Introduction

61 In 2009 Medicines360, a non-profit pharmaceutical company, initiated
62the ACCESS IUS (A Comprehensive Contraceptive Efficacy and Safety Study
63of an IUS) Phase-3 trial to assess efficacy and safety of a branded
64levonorgestrel 52mg intrauterine system (IUS) in a diverse population of U.S.
65women. Data supporting the 3- and 5-year approvals have been previously
66published [1,2]. In this evaluation, we report the data supporting a 6-year
67contraceptive indication.

2.0 Material and Methods

The ACCESS IUS study methodology, sample size rationale, Institutional Board Review, data analysis plans, and study population characteristics have been previously published [1,2]. The efficacy and safety data for this report includes all outcomes with levonorgestrel 52mg IUS (Liletta® [Medicines360, San Francisco, CA and Allergan, Irvine, CA]; Liletta® is a trademark of Odyssea Pharma SPRL [Belgium], an Allergan affiliate) use documented from the study start in December 2009 through August 20, 2018. Women in the efficacy evaluation (16-35 year olds) had at least one follow-up evaluation and a maximum duration of follow-up of 72 months (78 cycles). Duration of use for efficacy includes the time from IUS placement to the last in-office pregnancy test (or any reported positive test) for efficacy evaluations up to 6 years and to the last study contact for safety

evaluations. The study is ongoing, evaluating 16-35 year olds for up to 10 years and 36-45 year olds for up to 8 years of use.

The primary outcome of on-treatment pregnancy included any pregnancy with a conception date from the insertion date through seven days after IUS discontinuation. We calculated pregnancy rates primarily as the Pearl Index (number of pregnancies per 100 women-years); secondary efficacy outcomes include cumulative Pearl Indices over six years and life-table pregnancy rates calculated using the Kaplan-Meier method.

Amenorrhea, defined as no bleeding or spotting over a 90-day interval, was evaluated for the last 90-day interval in year 6 in participants with available bleeding questionnaire data. Safety analyses included any adverse events reported amongst all enrolled women regardless of duration of IUS use.

68 The Sponsor, Medicines360, designed the study and oversees its
69conduct, including funding the trial and providing study product free of
70charge to participants.

3.0 Results

71 Seventeen hundred fifty-one women (1600 at 16-35 years and 151 at
7236-45 years) enrolled and are included in the overall safety population; the
7316-35-year-old efficacy population included 1538 women. At the time of the
74data evaluation, 612 and 321 women in the efficacy population had
75completed 5 and 6 years of IUS use, respectively; 703, 402, 191 and 122

76women in the safety population had completed 5, 6, 7 and 8 years use,
77respectively. Table 1 presents efficacy per year and cumulatively over six
78years. Participants experienced no pregnancies in year 6. Amenorrhea in the
7990 days preceding the end of year 6 occurred in 141/349 (40.4%) women.

80 The most commonly reported adverse reactions over six or more years
81of use were vulvovaginal infections with bacteria (n=305, 17.4%) or yeast
82(n=291, 16.6%) or urinary tract infections (n=296, 16.9%). Of the 14 (0.8%)
83participants diagnosed with pelvic infection, two occurred after year 4 (one
84in year 6 and one in year 8).

85 Overall, 1132/1568 (72.2%) 16-35-year-olds and 122/146 (83.6%) 36-
8645-year-olds who received an IUS discontinued study participation. The most
87frequent discontinuation reasons among the 1714 women with successful
88insertion were an adverse event (n=329, 19.2%), seeking pregnancy
89(n=265, 15.5%), loss-to follow-up or withdrawal of consent (n=259, 15.1%),
90or relocation far from a study site (n=111, 6.5%). In the 36-45 year olds,
9145/122 (36.9%) discontinuations occurred because of mandatory study exit
92after 8 years of use for this group.

93 Of the 329 women who discontinued due to an adverse event, the
94most frequent event was partial or complete expulsion (n=68 [4.0%]) with 2
95expulsions per year in years 6 and 7 (all partial expulsions). Forty (2.3%)
96women discontinued for a bleeding complaint, with one in year 6 and none
97thereafter. Table 2 describes non-expulsion adverse events that resulted in

98at least 0.5% of women requesting discontinuation through six or more years
99of IUS use.

4.0 Discussion

100 The levonorgestrel 52mg IUS evaluated in this study is highly effective
101for contraception through six years. The safety profile through 6 or more
102years demonstrated a low discontinuation rate for adverse events. These
103results represent the largest evaluation of a levonorgestrel 52mg IUS in U.S.
104women for more than 5 years, with sufficient numbers of subjects to meet
105FDA-approval guidelines as detailed in a prior publication [1].

106 The safety data in this report include women who have used the
107levonorgestrel 52mg IUS for six or more years. The findings remain similar to
108those in the previously published 5-year efficacy and safety report [2].
109Beyond year 5, the number of expulsions or pelvic infections remains very
110low, indicating the infrequent occurrence of new significant events with
111extended use. Amenorrhea remains constant at about 40% at the end of
112year 6, similar to the rate seen from year 3 onward [2].

113 In 2016, the World Health Organization reported on use of a
114levonorgestrel 52mg IUS to seven years [3]. In that study, 1884 parous
115women 16-40 years old had a levonorgestrel 52mg IUS placed and had at
116least one follow-up visit at 11 Chinese (1062 subjects) and nine non-Chinese
117(822 subjects) multinational sites (locations not reported). Overall, 601
118women used the IUS for seven full years. The authors reported no

119pregnancies after year 5 with a 7-year life-table pregnancy rate of 0.5%.

120However, non-Chinese centers contributed only 178 women who completed
121seven years of use with a 7-year life-table pregnancy rate of 0.3%.

122Additionally, the efficacy calculation included women older than 35 years at
123enrollment.

124 We have few data about effectiveness after five years in non-Chinese
125populations. McNicholas et al [4] reported 496 women in St. Louis county
126who extended levonorgestrel 52mg IUS use past year 5 in follow-up from the
127CHOICE study. This study also included women 35 years or older at
128enrollment, comprising one-third of the women choosing extended use. The
129characteristics of the 347 women who completed 6 years of use are not
130described. The investigators reported one pregnancy in year 6 with a
131pregnancy rate of 0.25 (95% CI 0.04-1.42).

132 This pivotal Phase 3 study provides the most robust information to
133date on the clinical efficacy of a levonorgestrel 52mg IUS beyond 5 years in a
134young and diverse population. The study is planned to continue through 10
135years based on hormone release rates through five years [5]. As
136levonorgestrel 52mg IUS use continues beyond six years, we will continue to
137learn more about prolonged efficacy and how U.S. women perceive any
138potential bleeding pattern changes and other effects.

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157Table 1. Pregnancy rate through six years of levonorgestrel 52mg IUS use in U.S. women 16-35 years
158 old at insertion

Year	# 28-day cycles	# Pregnancies (total / ectopic)	Pearl Index Individual Year [pregnancies/100 women-years (95% CI)]	Pearl Index Cumulative [pregnancies/100 women-years (95% CI)]	Life-Table Pregnancy Rate [% (95% CI)]
1*	17,175	2 / 1	0.15 (0.02-0.55)	0.15 (0.02-0.55)	0.14 (0.04-0.57)
2	14,205	4 / 3	0.37 (0.10-0.94)	0.25 (0.09-0.54)	0.49 (0.22-1.09)
3	11,760	1 / 1	0.11 (0.00-0.62)	0.21 (0.08-0.43)	0.59 (0.28-1.25)
4	9,891	1 / 1	0.13 (0.00-0.73)	0.20 (0.08-0.39)	0.72 (0.36-1.45)
5	8,335	1 / 0	0.16 (0.00-0.87)	0.19 (0.09-0.36)	0.87 (0.44-1.70)
6 ⁺	5,091	0 / 0	0.00 (0.00-0.94)	0.18 (0.08-0.33)	0.87 (0.44-1.70)

159

160

161CI: Confidence Interval

162* One pregnancy following perforation and one pregnancy following complete expulsion – both in Year 1

163⁺ 229 women still active in Year 6 at the time of analysis

164Table 2. Non-expulsion-related adverse events* resulting in discontinuation in U.S. women using a
 165 levonorgestrel 52mg IUS for six or more years [n (%)][†]
 166

	Total (N=1,751)	16-35 Years Old (n=1,600)	36-45 Years Old (n=151)
Bleeding complaints	40 (2.3)	34 (2.1)	6 (4.0)
Acne	25 (1.4)	24 (1.5)	1 (0.7)
Dysmenorrhea	18 (1.0)	17 (1.1)	1 (0.7)
Weight increase	18 (1.0)	17 (1.1)	1 (0.7)
Mood swings	14 (0.8)	12 (0.8)	2 (1.3)
Uterine spasm (pain)	13 (0.7)	12 (0.8)	1 (0.7)
Pelvic discomfort or pain	10 (0.6)	10 (0.7)	0
Dyspareunia	10 (0.6)	9 (0.6)	1 (0.7)

167

168IUS = intrauterine system

169* Frequency $\geq 0.5\%$

170[†] Population is all women in which IUS placement was attempted; 32 women 16-35 years and 5 women
 171 36-45 years at enrollment did not have successful IUS placement