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Brief Research Article

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

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Conflicts of Interest: Carolyn L. Westhoff has served on Data Safety Monitoring Boards for studies sponsored by Bayer and Merck & Co, on an Advisory Board for Agile Therapeutics, and has been a consultant for Mithra. Her university department receives contraceptive research funding from Sebela, and Medicines360. Lisa M. Keder has served as a consultant for Bayer and trainer for Merck & Co. Her university department receives contraceptive research funding from Bayer, Medicines360, and Sebela. Angelina Gangestad has served on an advisory board for Bayer Healthcare. Her university department receives contraceptive research funding from Agile, Bayer Healthcare, Femasys and Medicines360. Stephanie B. Teal has served on a Data Safety and Monitoring Board for Merck & Co. Her university department receives contraceptive research funding from Bayer HealthCare, Medicines360, Merck & Co., and Sebela. Andrea I. Olariu is a Medicines360 employee. Mitchell D. Creinin has served on Advisory Boards for Lupin and Merck & Co. He has been a consultant for Danco, Estetra, Exeltis and Medicines360, and his university department receives contraceptive research funding from Daré Bioscience, HRA Pharma, Medicines360, Merck & Co., and Sebela.

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Abstract

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

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

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

Conclusion: This levonorgestrel 52mg IUS is a highly effective and safe contraceptive 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.

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

1.0 Introduction

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

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

3.0 Results

Seventeen hundred fifty-one women (1600 at 16-35 years and 151 at 36-45 years) enrolled and are included in the overall safety population; the 16-35-year-old efficacy population included 1538 women. At the time of the data evaluation, 612 and 321 women in the efficacy population had completed 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

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

4.0 Discussion

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

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

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

pregnancies after year 5 with a 7-year life-table pregnancy rate of 0.5%. However, non-Chinese centers contributed only 178 women who completed seven years of use with a 7-year life-table pregnancy rate of 0.3%. Additionally, the efficacy calculation included women older than 35 years at enrollment.

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

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

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Table 1. Pregnancy rate through six years of levonorgestrel 52mg IUS use in U.S. women 16-35 years 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)

CI: Confidence Interval

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

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

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

	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)

IUS = intrauterine system

* Frequency ≥0.5%

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