

Meilensteine der Kontrazeption

- Die Pille 1960
- Die Kupferspirale 380 mm² 1988
- Die Hormonspirale 1990
- Jaydess 2013

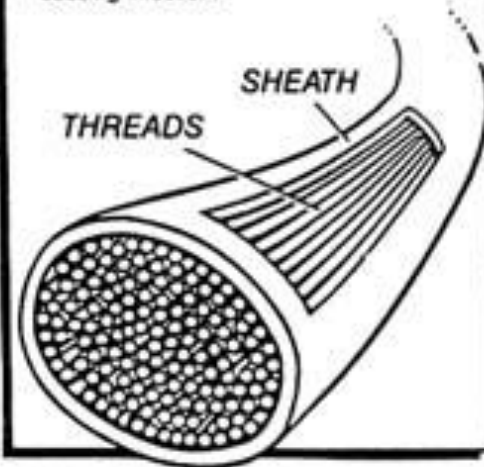
DALKON SHIELD

UTERUS



THE DALKON SHIELD STRING

A cross-section of the Dalkon Shield tail string showing the hundreds of tiny threads within the sheath. Bacteria climb between these threads from the vagina into the uterus, causing infection.



VAGINA

THE LEGACY OF THE SHIELD

More than 2 million U.S. women used the device between 1971 and 1974 when it was removed from the market. Another 800,000 women in other countries also used shields.

Thousands suffered pelvic infections, hundreds had spontaneous abortions because of infections, and at least 18 U.S. women died.

More than 12,000 women have sued or brought claims against the manufacturer, A. H. Robins Co. In the first quarter of this year an average of ten new cases a day has been filed against the company.

FEBRUARY 27, 2012, 3:45 PM | 140 Comments

Americans Get Reacquainted With IUDs

By JANE E. BRODY

After decades of sloppy research, bad publicity, lawsuits and widespread fears of health hazards, the intrauterine device is making a major comeback in the United States.

Although the IUD has long been the most popular reversible form of contraception worldwide, use of the device in this country, where oral contraceptives have always been far more popular, has lagged far behind that in other industrialized nations.



Nach Jahrzehnten schlampiger Forschung, schlechter Publicity, Rechtsstreitigkeiten und weit verbreiteter Angst vor gesundheitlichen Gefahren, hat die Spirale in den Vereinigten Staaten ein großes Comeback.

History of Mirena[®]: Professor Tapani Luukkainen had the idea to develop a progestin-releasing IUS for contraception

- 1970: Ford Foundation awarded the University of Helsinki a 5-year grant for progestin-related research and development of long-acting reversible contraception (LARC) methods
- The Family Planning Clinic of the Maternity Hospital in Helsinki and the Steroid Research Laboratory at the University of Helsinki started co-operation to develop a levonorgestrel-releasing intrauterine system (IUS)



ORIGINAL ARTICLE

Effectiveness of Long-Acting Reversible Contraception

Brooke Winner, M.D., Jeffrey F. Peipert, M.D., Ph.D., Qihong Zhao, M.S.,
Christina Buckel, M.S.W., Tessa Madden, M.D., M.P.H., Jenifer E. Allsworth, Ph.D.,
and Gina M. Secura, Ph.D., M.P.H.

ABSTRACT

BACKGROUND

The rate of unintended pregnancy in the United States is much higher than in other developed nations. Approximately half of unintended pregnancies are due to contraceptive failure, largely owing to inconsistent or incorrect use.

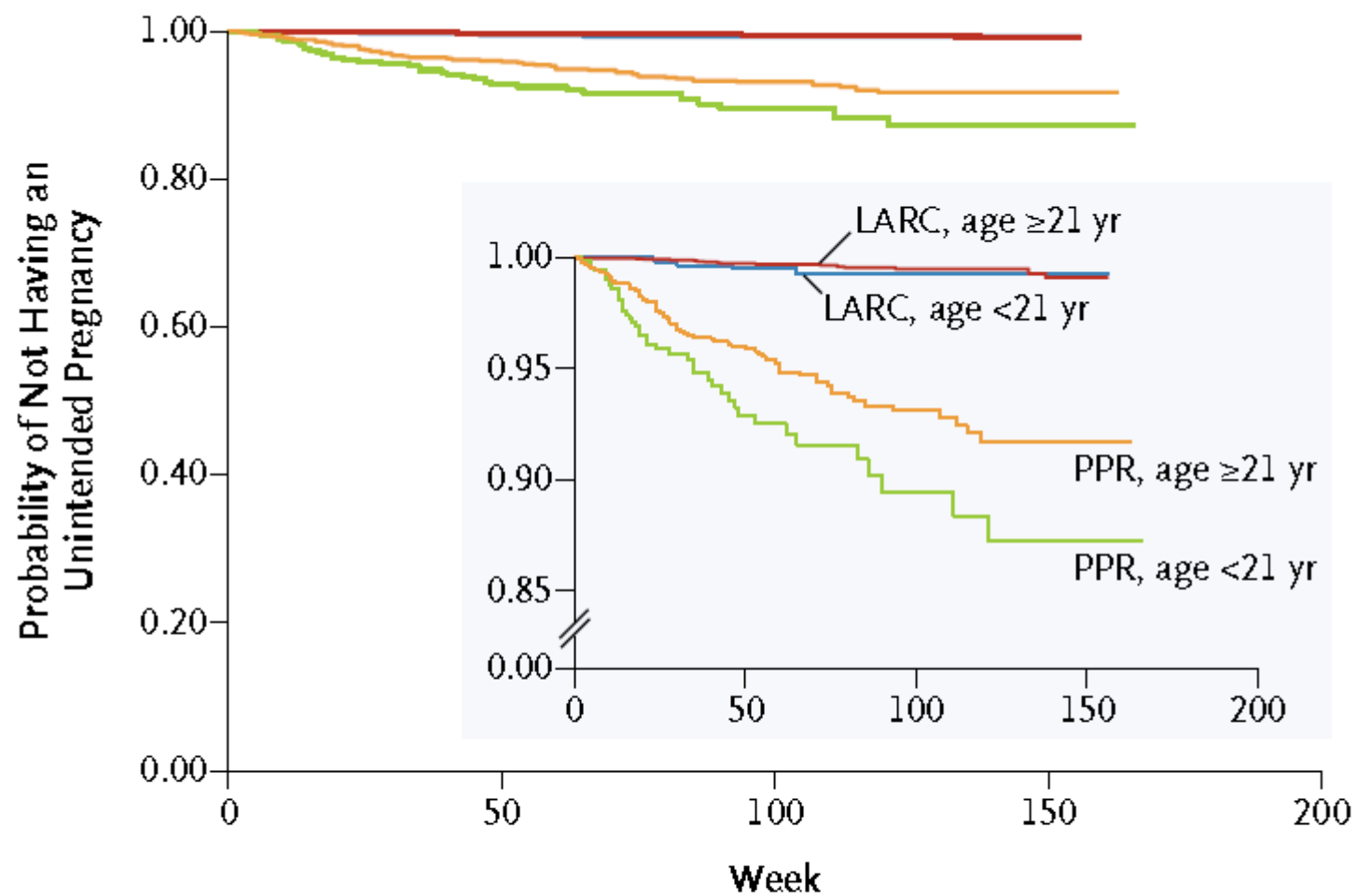


Figure 2. Probability of Not Having an Unintended Pregnancy, According to Contraceptive Method and Age.

Reversible Langzeit-Verhütungsmethoden

Long-acting reversible Contraception

LARC

- **Erster Geschlechtsverkehr**
- **durchschnittlich**
- **mit 16 Jahren**

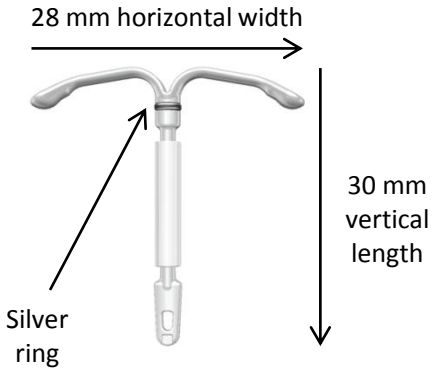
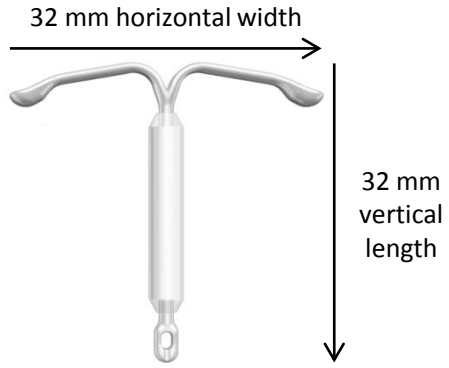


- **Erstes Kind**
- **durchschnittlich**
- **mit 29 Jahren**



- **Längere Ausbildung**
- **Sicherheit & Komfort**

Jaydess[®]/Skyla[®]: Small T-body with narrow insertion tube and a low dose

	Jaydess ^{®1}	Mirena ^{®2}
T-frame dimensions	 <p>28 mm horizontal width</p> <p>30 mm vertical length</p> <p>Silver ring</p>	 <p>32 mm horizontal width</p> <p>32 mm vertical length</p>
Insertion tube diameter, mm	3.80 (with EvolInserter [™])	4.75 ¹ (with Mirena [®] introducer ^a)
Initial <i>in vivo</i> LNG release rate, µg/day	14 (24 days after placement)	20 (not same timepoint or calculation model)
Maximum duration of use, years	3	5
Total LNG content, mg	13.5	52

^aThe Mirena[®] EvolInserter[™], which has a diameter of 4.40 mm, is now available in some countries
LNG, levonorgestrel

1. Bayer HealthCare Pharmaceuticals, 2013; 2. Bayer HealthCare Pharmaceuticals, 2009

Langjährige Erfahrung mit Mirena®

Mirena® ist seit **17** Jahren in Österreich
und seit **23** Jahren weltweit am Markt.¹

Mirena® ist weltweit in **131** Ländern erhältlich.¹

Mirena® ist eines der meist untersuchten Produkte
mit mehr als **4.700** peer-reviewed
wissenschaftlichen Studien seit dem Launch.²

Zwei große post-launch Studien mit über **17.000**
und **43.000** Frauen haben die hohe kontrazeptive
Zuverlässigkeit in der "Real Life" - Anwendung bestätigt.³



¹ Bayer HealthCare Pharmaceuticals, Mirena® Product Monograph 2014

² Reference to >4700 peer-reviewed scientific publications based on search in Pub Med database May 2014 Keyword: Mirena®

³ Beckman T, Rauramo J, Huhtala S, Koskenvuo M. Pregnancy during the use of levonorgestrel intrauterine system. Am J Obstet Gynecol 2004; Jan;190(1):50-4



LAT/1.2015.1437

Table 10. Overview of Jaydess® clinical development program

Study	Design	Population	Study drug(s)	Main outcomes	Timeframe
308901 Dose finding over 3 years of use (EU) (Phase II) ⁵¹	Multicenter, open-label, randomized, controlled, three-arm, parallel group	Nulliparous and parous women aged 21–40 years, n=742*	Jaydess®, LNG-IUS 19.5 mg, and Mirena®	Primary: Dose-finding study to select a dose for Phase III testing (this study was not powered to calculate the PI)	Complete
310442 Efficacy and safety of Jaydess® over 3 years of use (5 years for LNG-IUS 19.5 mg) (EU, NA, LA) (Phase III) ⁵²	Multicenter, open-label, randomized, two-arm, parallel group	Nulliparous and parous women aged 18–35 years, n=2,885	Jaydess® and LNG-IUS 19.5 mg	Primary: PI Secondary: bleeding profile, safety, pharmacokinetics, user satisfaction	3-year study complete (2-year extension phase for LNG-IUS 19.5 mg is ongoing)
311966 Asia-Pacific Study (China, Australia, Korea) (NCT00884260)	Multicenter, single-arm	Nulliparous and parous women aged 18–40 years, n=918	Jaydess®	Primary: PI Secondary: expulsion rates, discontinuation rates, AEs, laboratory tests	June 2013
13362 Profiling 1 study Jaydess® vs COC user satisfaction study (NCT01254292)	Multicenter, open-label, randomized, two-arm, parallel group, 18 months	Nulliparous and parous women aged 18–29 years, n=567	Jaydess® and Yasmin®	Primary: User satisfaction. Secondary: PI, tolerability, discontinuation rates, expulsion rates, ease/pain of placement/removal, treatment-related AEs	June 2014
13363 Profiling 2 study Jaydess® vs Nexplanon® (NCT01397097)	Multicenter, open-label, randomized, two-arm, parallel group, 12 months + extension up to 3 years (Jaydess® arm only)	Nulliparous and parous women aged 18–35 years, n=766	Jaydess® and Nexplanon®	Primary: discontinuation rates. Secondary: discontinuation rates by reason, satisfaction, PI	June 2015
14371 Adolescent safety and tolerability study (NCT01434160)	Multicenter, open-label, single-arm study, 12 months + extension up to 3 years	Nulliparous and parous women, post-menarcheal, aged <18 years, n=304	Jaydess®	Primary: AE frequency, proportion of women reporting AEs. Secondary: satisfaction, PI, bleeding patterns, LNG and SHBG concentration in serum,	July 2015

*Includes four women with failed placements who were not included in the full analysis set for this study.

⁵¹Nexplanon® is a registered trademark of Merck & Co., Inc.

AE, adverse event; COC, combined oral contraceptive; EU, European Union; LA, Latin America; LNG, levonorgestrel; NA, North America; PI, Pearl Index; SHBG, sex hormone-binding globulin.

ORIGINAL ARTICLE: CONTRACEPTION

**Fertility
and Sterility.**



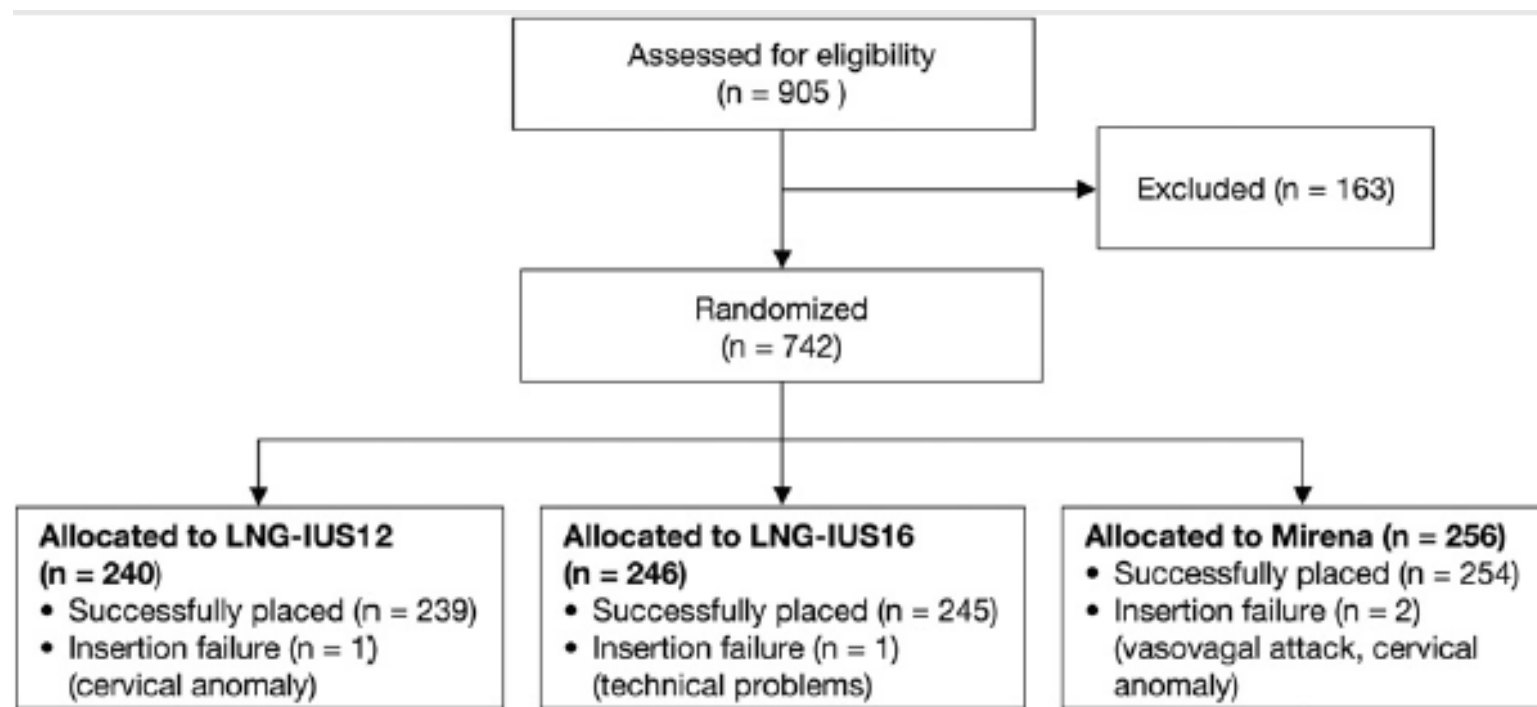
Fertility and Sterility® Vol. -, No. -, - 2012

A randomized, phase II study describing the efficacy, bleeding profile, and safety of two low-dose levonorgestrel-releasing intrauterine contraceptive systems and Mirena

Kristina Gemzell-Danielsson, M.D., Ph.D.,^a Ilka Schellschmidt, M.D.,^b and Dan Apter, M.D., Ph.D.^c

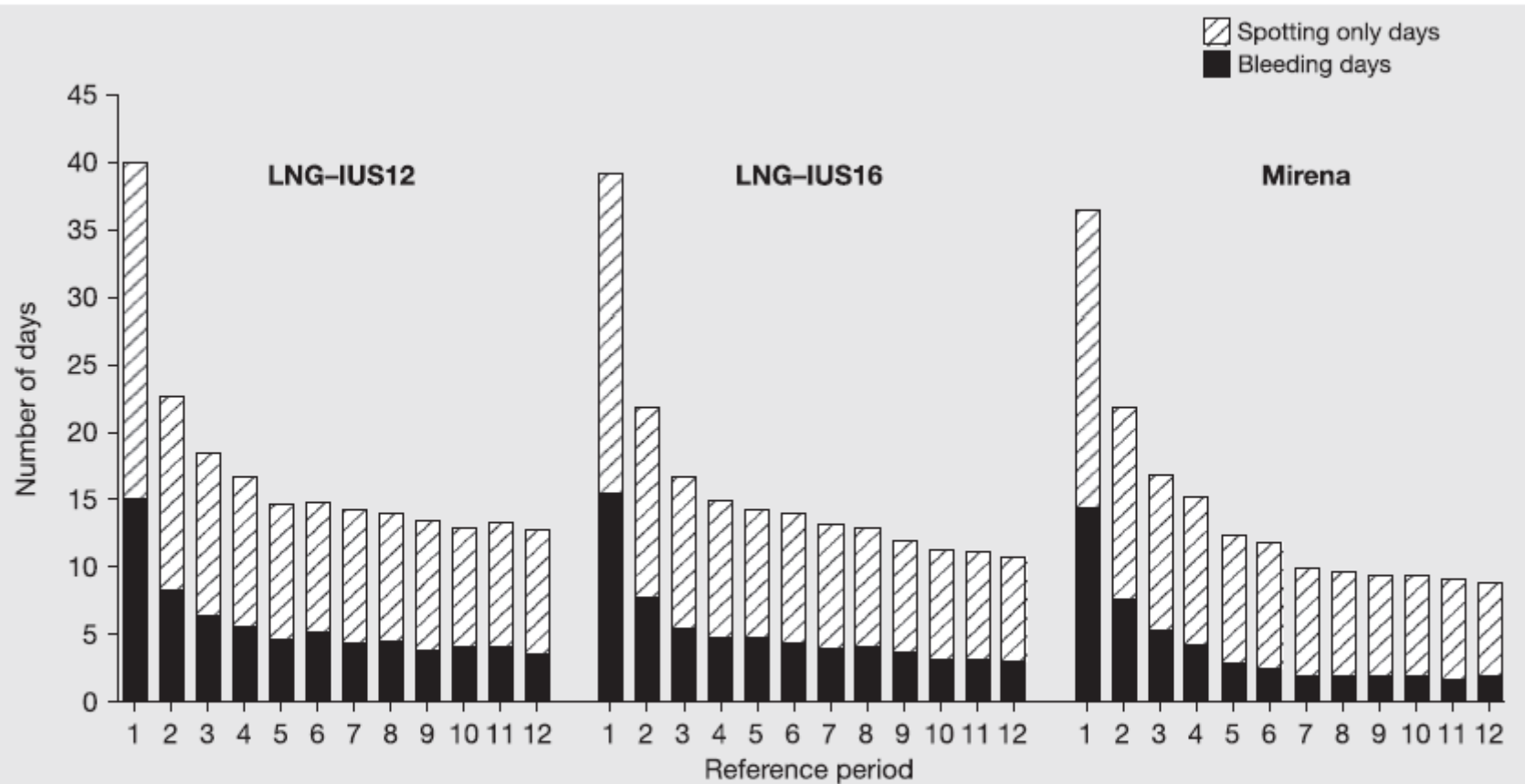
^a Division of Obstetrics and Gynecology, Department of Women's and Children's Health, Karolinska Institutet/Karolinska University Hospital, Stockholm, Sweden; ^b Bayer, Global Medical Affairs Women's Health, Berlin, Germany; and ^c Sexual Health Clinic, Väestöliitto, Helsinki, Finland

A randomized, phase II study describing the efficacy, bleeding profile, and safety of two low-dose levonorgestrel-releasing intrauterine contraceptive systems and Mirena



A randomized, phase II study describing the efficacy, bleeding

FIGURE 1



Mean number of bleeding or spotting days per 90-day reference period during the 3 years of the intrauterine system use (reference periods 1–12). Drop-outs were not accounted for in this analysis; the results are based on subjects participating during the respective reference period. The drop-out rates (for any reason) were 27.2%, 29.0%, and 28.3% in the LNG-IUS12, LNG-IUS16, and Mirena arms, respectively. It is possible that subjects dropping out as a result of changes in bleeding patterns may have influenced these results. LNG-IUS = levonorgestrel intrauterine system.

A randomized, phase II study describing the efficacy, bleeding profile, and safety of two low-dose levonorgestrel-releasing intrauterine contraceptive systems and Mirena

SUPPLEMENTAL TABLE 2

Ease and pain of insertion of LNG-IUS12 and LNG-IUS16 compared with Mirena (full analysis set: all randomized subjects with a successful placement).

	LNG-IUS12 (n = 239)	LNG-IUS16 (n = 245)	Mirena (n = 254)
Investigators' evaluation of placement			
Easy	226 (94.6%)	229 (93.5%)	219 (86.2%)
Slightly difficult	11 (4.6%)	14 (5.7%)	31 (12.2%)
Very difficult	2 (0.8%)	2 (0.8%)	4 (1.6%)
P-value for overall difference vs. Mirena ^a	<.01	.02	
Subjects' evaluation of pain of placement			
None	72 (30.1%)	65 (26.5%)	44 (17.3%)
Mild	101 (42.3%)	112 (45.7%)	103 (40.6%)
Moderate	53 (22.2%)	59 (24.1%)	90 (35.4%)
Severe	12 (5.0%)	9 (3.7%)	17 (6.7%)
Not done	1 (0.4%)	0 (0)	0 (0)
P-value for overall difference vs. Mirena ^a	<.001	<.01	

Note: LNG-IUS = levonorgestrel intrauterine system.

^a P-values from pairwise comparison by Fisher's exact test.

Gemzell-Danielsson. Efficacy and safety of two new LNG-IUSs. *Fertil Steril* 2012.

A randomized, phase II study describing the efficacy, bleeding profile, and safety of two low-dose

TABLE 3

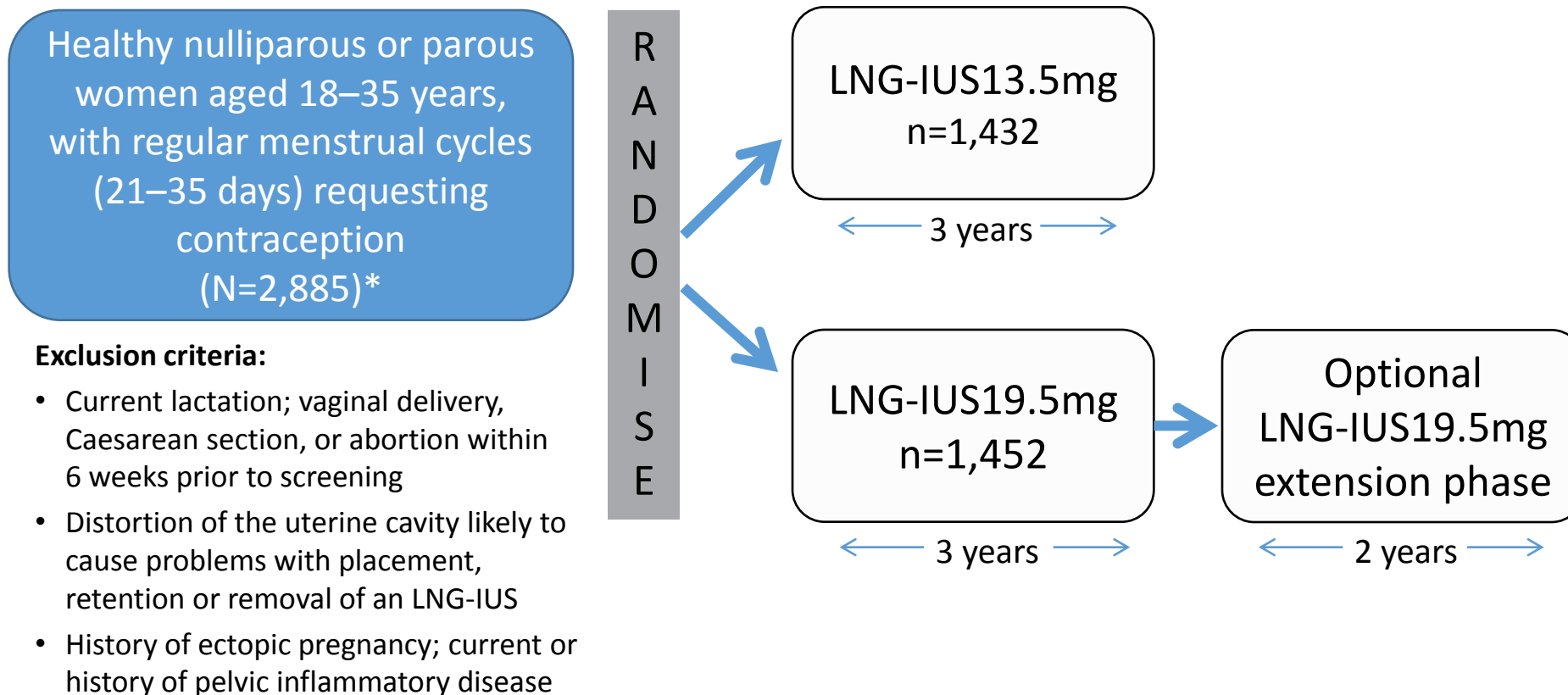
Most frequently reported treatment-related adverse events (reported by ≥ 10 women in full analysis set) by frequency of occurrence.

MedDRA preferred term	LCS12 (n = 239) n (%) Jaydess®	LCS16 (n = 245) n (%)	Mirena (n = 254) n (%) Mirena®	Total (n = 738) n (%)
Progestin related AEs				
Headache	28 (11.7)	32 (13.1)	44 (17.3)	104 (14.1)
Nausea	13 (5.4)	14 (5.7)	17 (6.7)	44 (6.0)
Altered mood	34 (14.2)	25 (10.2)	25 (9.8)	84 (11.4)
Edema	10 (4.2)	17 (6.9)	17 (6.7)	44 (6.0)
Acne	62 (25.9)	55 (22.4)	72 (28.3)	189 (25.6)
Seborrhea	16 (6.7)	18 (7.3)	20 (7.9)	54 (7.3)
Breast pain	15 (6.3)	28 (11.4)	18 (7.1)	61 (8.3)
Breast discomfort	46 (19.2)	45 (18.4)	57 (22.4)	148 (20.1)
Increased weight	27 (11.3)	28 (11.4)	21 (8.3)	76 (10.3)
Bleeding related AEs				
Dysmenorrhea	12 (5.0)	12 (4.9)	11 (4.3)	35 (4.7)
Vaginal hemorrhage	9 (3.8)	2 (0.8)	4 (1.6)	15 (2.0)
Infections				
Vaginal infection	5 (2.1)	4 (1.6)	5 (2.0)	14 (1.9)
Vulvovaginal candidiasis	10 (4.2)	5 (2.0)	6 (2.4)	21 (2.8)
Vaginitis bacterial	6 (2.5)	1 (0.4)	3 (1.2)	10 (1.4)
Other AEs				
Ovarian cyst ^a	14 (5.9)	21 (8.6)	56 (22.0)	91 (12.3)
Abdominal distention	33 (13.8)	35 (14.3)	41 (16.1)	109 (14.8)
Abdominal pain	13 (5.4)	11 (4.5)	14 (5.5)	38 (5.1)
Lower abdominal pain	8 (3.3)	10 (4.1)	11 (4.3)	29 (3.9)
Procedural pain	4 (1.7)	4 (1.6)	3 (1.2)	11 (1.5)

Note: Subjects were specifically asked at each study visit whether they experienced hormone-related adverse events. AE = adverse event.

^a Cysts described as abnormal, nonfunctional, and/or >3 cm in diameter.

Phase III study design



*One woman was randomised but no insertion was attempted; therefore, she was excluded from the full analysis set of 2,884 women
Treatment allocation was blinded to women, but not to investigators
This presentation shows data from the 3-year study and not from the extension study

Phase III study: Jaydess[®] was highly effective, with a 3-year Pearl Index of 0.33

- Kaplan–Meier estimate for the cumulative failure rates: 0.4% at 1 year

Time	Relevant exposure, WY	Pregnancies, n	Pearl Index	95% CI
Year 1	1,217.78	5	0.41	0.13–0.96 ^a
Year 2	1,015.67	3	0.30	0.06–0.86 ^a
Year 3	825.17	2	0.24	0.03–0.88 ^a
2 years	2,233.45	8	0.36	0.15–0.71
3 years	3,058.62	10	0.33	0.16–0.60

^a95% CIs overlap

Relevant exposure was calculated from the total exposure minus the time in which back-up contraception (e.g. condoms) was used or sex hormones were taken for other reasons

CI, confidence interval; WY, woman-years

Bayer HealthCare Pharmaceuticals, 2013; Bayer HealthCare Pharmaceuticals, 2011

	Jaydess	Mirena
Liegedauer	3 Jahre	5 Jahre
Größe	28*30 mm	32*32 mm
Durchmesser des Insertionsröhrchens	3,8 mm	4,8 mm (EvoInserter™ 4,45mm)
Indikation	Kontrazeption	Kontrazeption, Hypermenorrhoe, Endometriumprotektion bei HRT
Pearl Index	0,41 (0,33 nach 3 Jahren)	0,2 Mirena
Hormongehalt gesamt	13,5mg	52mg
Tägliche Hormonabgabe Beginn/Ende der Anwendung	14µg/d → 5µg/d	20µg/d → 10µg/d
LNG-Serumspiegel Beginn/Ende der Anwendung	162pg/ml → 59pg/ml	206pg/ml → 131pg/ml
Ovulationshemmung	Praktisch nicht; kein Einfluss auf Ovarialfunktion & Östrogenspiegel	Bei einigen Frauen
Amenorrhoeerate	11,6 %	20%
Detektion	Röntgendicht durch Bariumsulfat & bessere Sichtbarkeit im Ultraschall durch Silberring	Röntgendicht durch Bariumsulfat
Besonderheiten	Signifikant weniger Ovarialzysten unter der Anwendung	

Original research article

Quantitative levonorgestrel plasma level measurements in patients with regular and prolonged use of the levonorgestrel-releasing intrauterine system[☆]

Beata Seeber^a, Stephanie C. Ziehr^a, Aandrea Gschließer^{a,b,1}, Christina Moser^c, Verena Mattle^a, Christoph Seger^c, Andrea Griesmacher^c, Nicole Concin^b, Hans Concin^d, Ludwig Wildt^{a,*}

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Received 3 August 2011; revised 21 January 2012; accepted 27 January 2012

Abstract

Background: The levonorgestrel-releasing intrauterine system (LNG-IUS) is well accepted as an easy-to-use contraceptive with an excellent side-effect profile. It contains a reservoir of 52 mg of levonorgestrel (LNG) with continuous release of the steroid. Its contraceptive use is approved for 5 years. The aim of this study was to determine the plasma concentration of LNG and its variation with time in patients with in-dwelling LNG-IUS Mirena®.

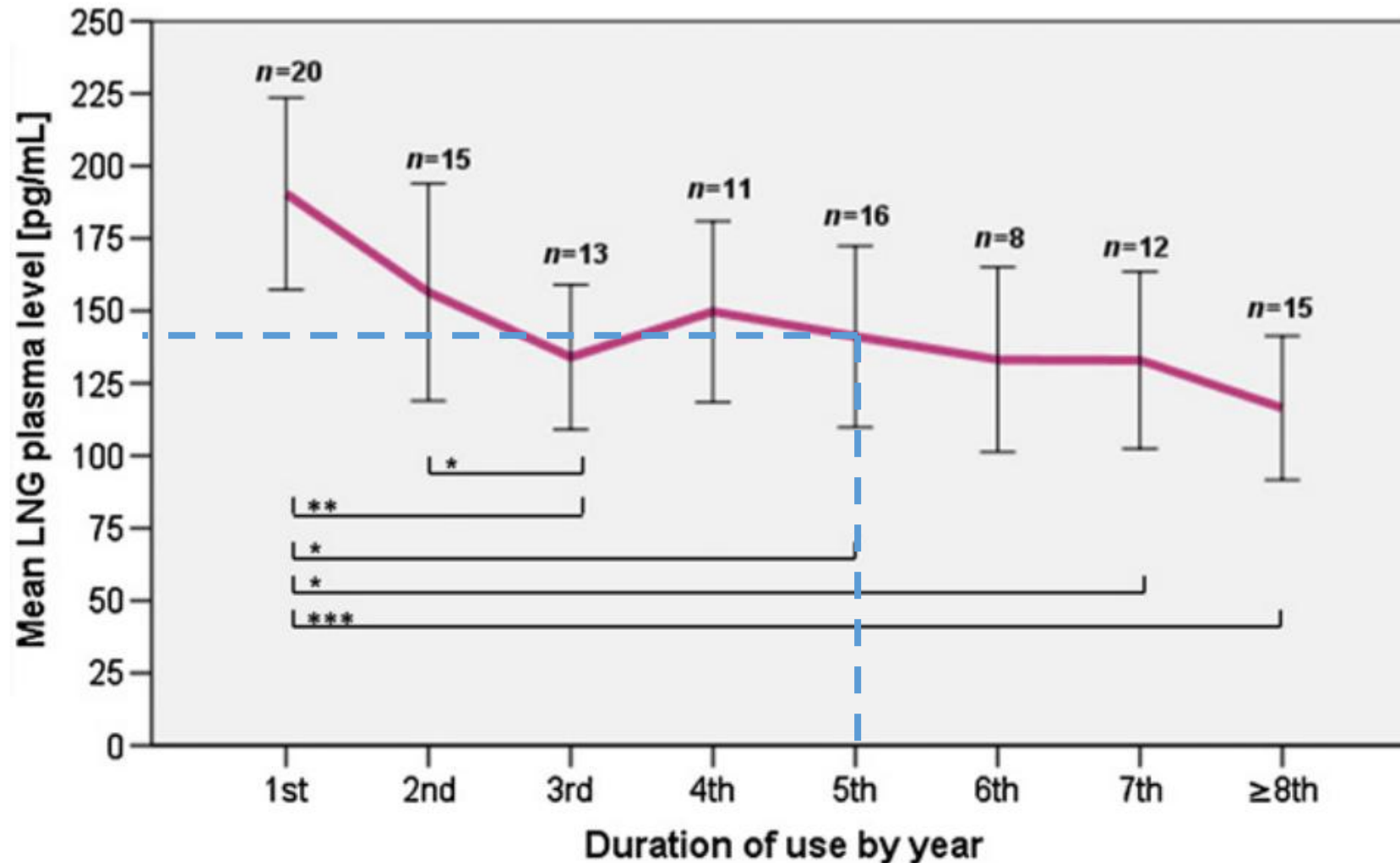
Study Design: In this study, we determined LNG plasma concentrations in 110 women with LNG-IUS at different time points of use. Time from insertion of the system in the study population ranged from 20 days to 11.1 years. Quantitative LNG levels were determined using a validated liquid chromatography–tandem mass spectrometry assay.

Results: The mean±SD LNG plasma level in all women was 147±59 pg/mL. A highly significant negative correlation between LNG plasma level and LNG-IUS time of use could be demonstrated. In the first year of use, LNG plasma level was as high as 191±71 pg/mL, decreasing to 157±68 pg/mL in the second year and 134±41 pg/mL in the third year. Even after exceeding the recommended period of LNG-IUS use, systemic LNG concentrations were detectable: 133±38 pg/mL in the sixth year, 133±48 pg/mL in the seventh year and 117±45 pg/mL in the eighth year. Furthermore, a significant negative correlation between LNG plasma level and body mass index could be shown.

Conclusion: Systemic LNG concentrations can be found in all patients with LNG-IUS IUS. However, concentrations are much lower than in other forms of LNG application. Moreover, this study demonstrates that a systemic effect of LNG-IUS can also be found after the recommended contraceptive lifespan of 5 years.

Quantitative levonorgestrel plasma level measurements in patients with regular and prolonged use of the levonorgestrel-releasing intrauterine system[☆]

Beata Seeber^a, Stephanie C. Ziehr^a, Aandrea Gschließer^{a,b,1}, Christina Moser^c, Verena Mattle^a, Christoph Seger^c, Andrea Griesmacher^c, Nicole Concin^b, Hans Concin^d, Ludwig Wildt^{a,*}

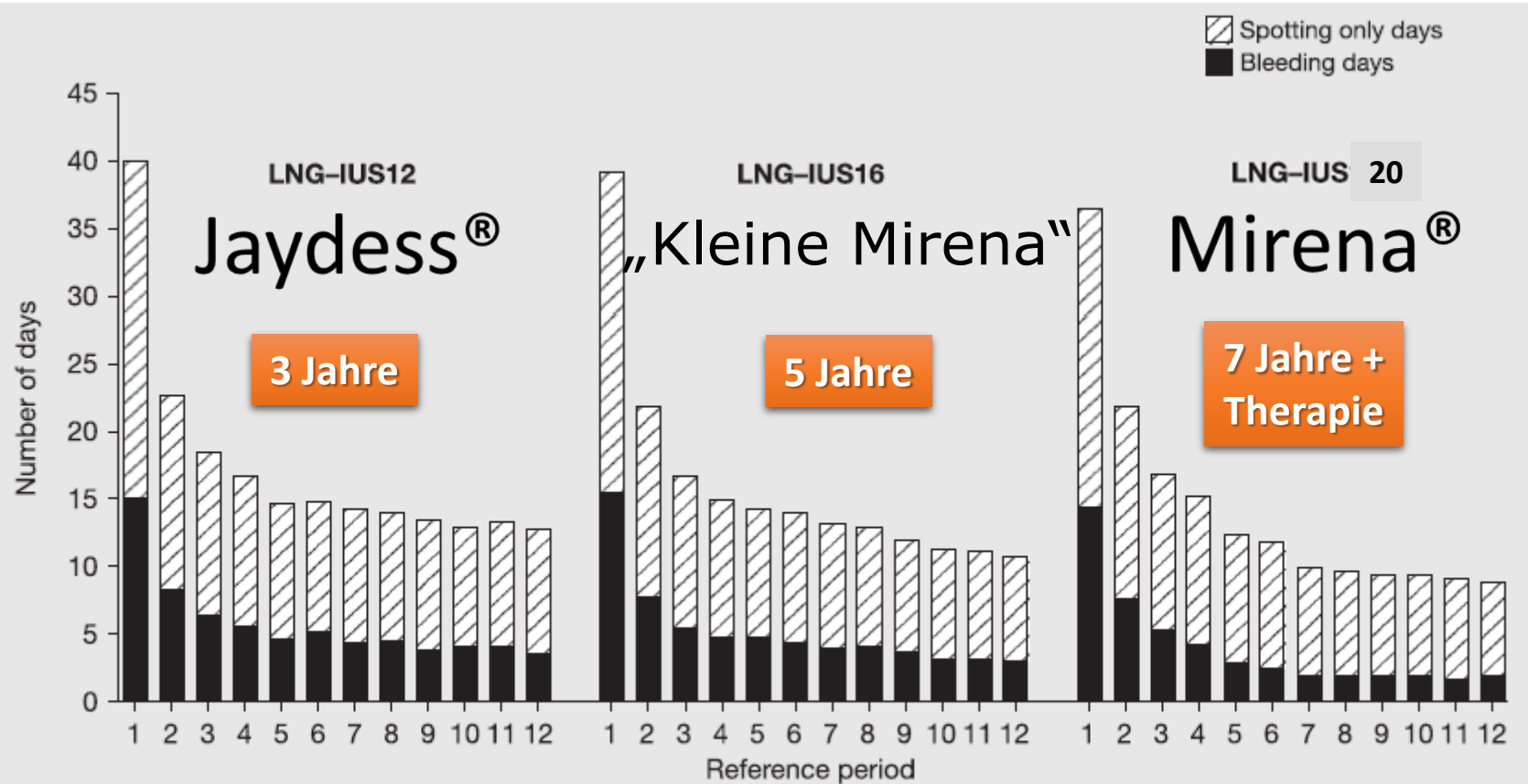


Mirena/Jaydess	Mirena Ibk/Breg	Brazil	Jaydess	Ameno. Mirena %
1. -2. Monat	206*	253	162*	
1. Jahr	191			~20
2. Jahr	157	pg/ml Levonorgestrel		~30
3. Jahr	134		59*	~40
6. Jahr	133			~50
7. Jahr	133	137		41,8
8. Jahr	117			
8,5 Jahre		119		31,5

* Firmenabgaben

A randomized, phase II study describing the efficacy, bleeding

FIGURE 1



Mean number of bleeding or spotting days per 90-day reference period during the 3 years of the intrauterine system use (reference periods 1–12). Drop-outs were not accounted for in this analysis; the results are based on subjects participating during the respective reference period. The drop-out rates (for any reason) were 27.2%, 29.0%, and 28.3% in the LNG-IUS12, LNG-IUS16, and Mirena arms, respectively. It is possible that subjects dropping out as a result of changes in bleeding patterns may have influenced these results. LNG-IUS = levonorgestrel intrauterine system.

AOGS REVIEW ARTICLE

Emerging indications for the levonorgestrel-releasing intrauterine system (LNG-IUS)

OSKARI HEIKINHEIMO¹ & KRISTINA GEMZELL-DANIELSSON²

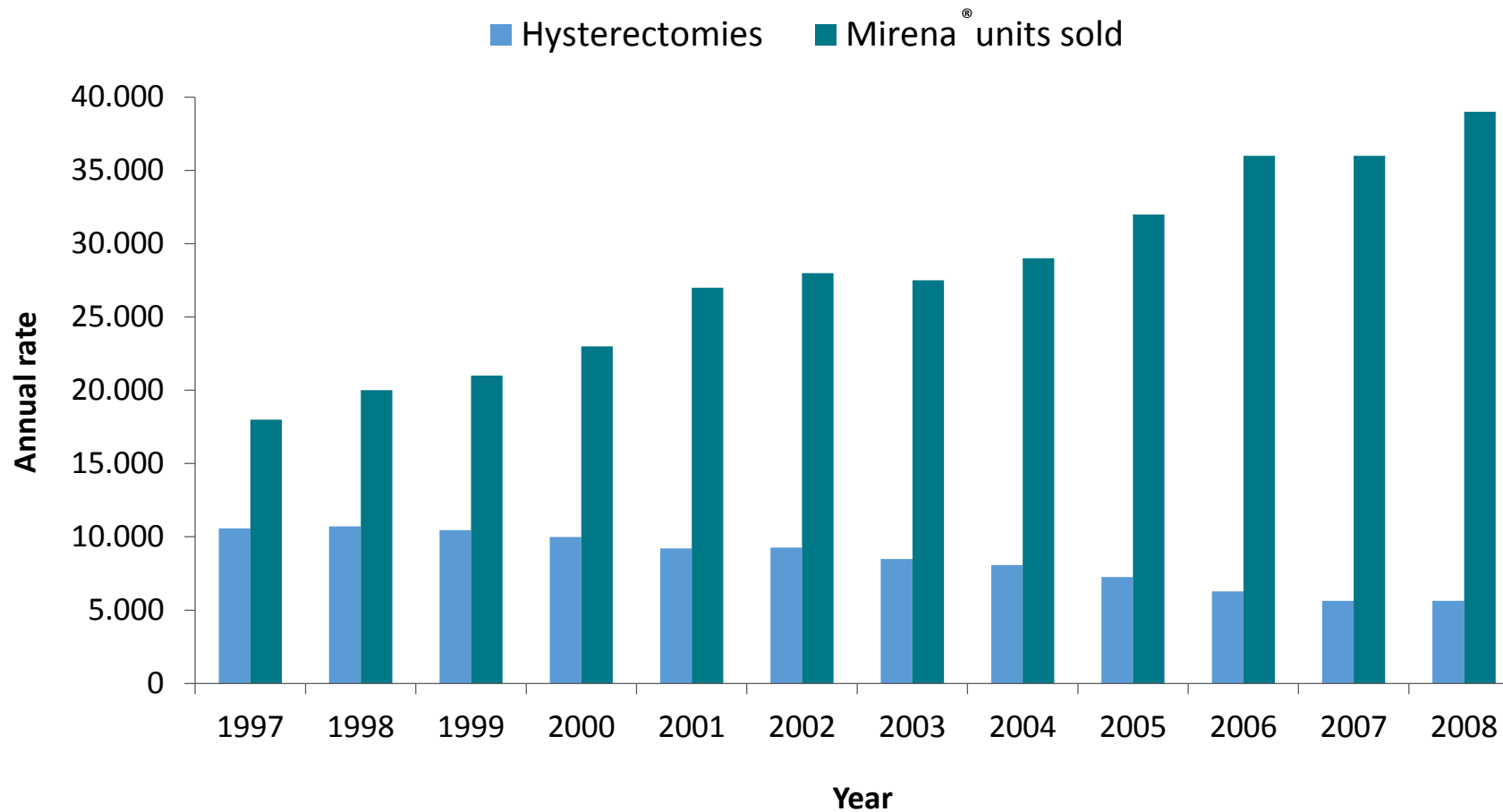
¹Department of Obstetrics and Gynaecology, University of Helsinki and Helsinki University Central Hospital, Helsinki, Finland, and ²Department of Women's and Children's Health, Division of Obstetrics and Gynecology, Karolinska Institutet/Karolinska University Hospital, Stockholm, Sweden

ERT
heavy menstrual bleeding
uterine fibroids
endometriosis
adenomyosis
dysmenorrhea
endometrial hyperplasias,
including atypical hyperplasia

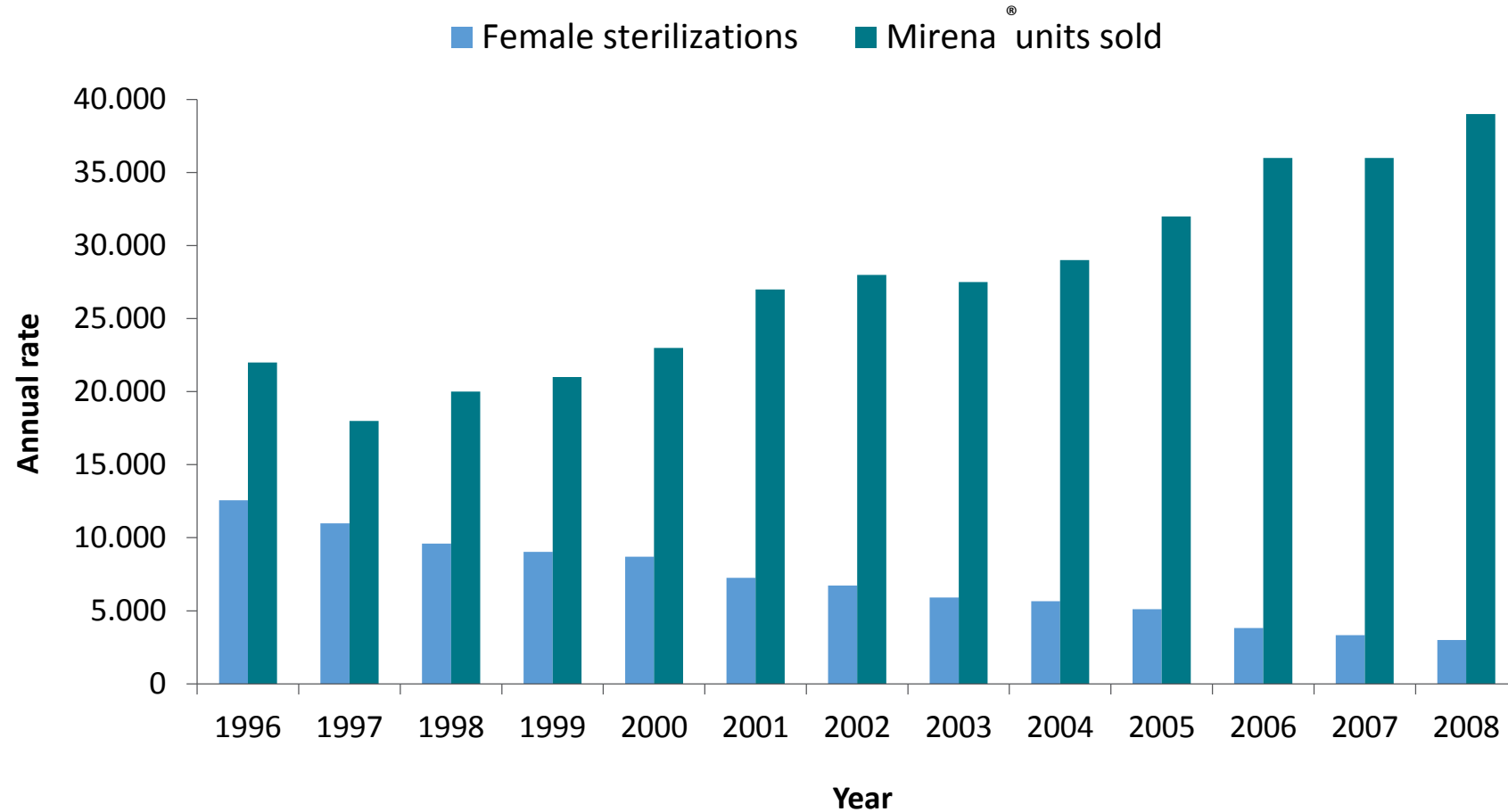
act as ad hoc invited speakers at scientific meetings for Bayer HealthCare Pharmaceuticals AG.

treatment with systemic progestins. Further studies are needed to examine the full potential of the LNG-IUS in such common clinical situations.

Reduction of hysterectomies in Finland after the introduction of Mirena[®]



As Mirena[®] uptake has increased in Finland, the number of female sterilizations has declined



Management of pain associated with the insertion of intrauterine contraceptives

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BACKGROUND: Most intrauterine contraception (IUC) placements do not require pain relief. However, small proportions of nulliparous (~17%) and parous (~11%) women experience substantial pain that needs to be proactively managed. This review critically evaluates the evidence for pain management strategies, formulates evidence-based recommendations and identifies data gaps and areas for further research.

METHODS: A PubMed literature search was undertaken. Relevant articles on management of pain associated with IUC insertion, published in English between 1980 and November 2012, were identified using the following search terms: 'intrauterine contraception', 'insertion' and 'pain'. RCTs were included; further relevant articles were also identified and included as appropriate.

RESULTS: Seventeen studies were identified and included: 12 RCTs and one non-randomized study of pre-insertion oral analgesia, cervical priming and local anaesthesia; one systematic review and one RCT on post-insertion analgesia and two non-randomized studies on non-pharmacological interventions. There was no conclusive evidence that any prophylactic pharmacological intervention reduces pain associated with IUC insertion. However, most of the regimens studied were adopted from hysteroscopy or abortion and effectiveness in specific subsets of women has not been studied adequately. A systematic review found non-steroidal anti-inflammatory agents (NSAID) to be effective in reactively treating post-insertion pain, but no benefit was found with prophylactic use.

CONCLUSIONS: No prophylactic pharmacological intervention has been adequately evaluated to support routine use for pain reduction during or after IUC insertion. Women's anxiety about the procedure may contribute to higher levels of perceived pain, which highlights the importance of counselling, and creating a trustworthy, unhurried and professional atmosphere in which the experience of the provider also has a major role; a situation frequently referred to as 'verbal anaesthesia'.

Key words: intrauterine contraception / pain / analgesia / local anaesthesia / cervical priming

Arthrotec-Manteltabletten

2. Qualitative und quantitative **Zusammensetzung**

1 Manteltablette enthält:

im magensaftresistenten Kern:

Diclofenac-Natrium 50 mg,

in der Ummantelung:

Misoprostol 200 µg.

Sonstiger Bestandteil mit bekannter Wirkung: Jede Manteltablette enthält 10 mg Lactose. Vollständige Auflistung der sonstigen Bestandteile siehe Tabelle 1.

3. **Darreichungsform**

Weiß, runde, bikonvexe Manteltabletten.

4. **KLINISCHE ANGABEN**

4.1 **Anwendungsgebiete**

Arthrotec-Manteltabletten sind angezeigt bei Patienten mit Schmerzen, die durch eine gastrointestinale Ulcera bedürfen.

Diclofenac ist angezeigt für die symptomatische Behandlung von Schmerzen.

A RANDOMIZED PHASE III STUDY COMPARING A NEW 13.5 MG LEVONORGESTREL INTRAUTERINE CONTRACEPTIVE SYSTEM WITH A COMBINED ORAL CONTRACEPTIVE: ANALYSIS OF EFFICACY AND BLEEDING PROFILES.

L. Borgatta,^a K. Roth,^b S. Ry
^a Boston University School

OBJECTIVE: To compare co
intrauterine contraceptive
(COC) in younger women.

DESIGN: A randomized Ph

MATERIALS AND METHODS: Nulliparous and parous women aged 18-29 years with regular menstrual cycles (21-35 days), requesting contraception, were randomized to use LNG-IUS13.5mg or COC for 18 months.

RESULTS: The full analysis set included **279 women randomized to LNG-IUS13.5mg** and who had a placement attempt (successful in 279) and **281 women randomized to COC** who took R1 pill. For LNG-IUS13.5mg and COC groups, respectively, the mean age was 23.7 years and 23.9 years, and **77.4% and 73.3% were nulliparous**. At Month 18/end of study, 70/247 COC users (28.3%) reported that they 'sometimes missed pills' and 132/247 (53.4%) reported that they 'sometimes took a pill late'. **There were 6 pregnancies in the COC group**; the unadjusted Pearl Index (PI) was approximately twice that of the adjusted PI (1.82 vs 0.91). By contrast, there were **2 pregnancies in the LNG-IUS13.5mg group**; the unadjusted and adjusted PIs were identical (0.57). The mean number of combined **bleeding and spotting days** declined over time in the LNG IUS13.5mg group, from **31.7 days in the first 90-day reference interval (RI) to 13.5 days in the sixth (final) 90-day RI**, but remained relatively constant during COC use (range: 15.6–19.2 per 90-day RI). By the final 90-day RI, for LNG-IUS13.5mg and COC users, respectively, **13.6% and 0.5% had amenorrhea**; 29.5% and 16.6% had infrequent bleeding; 21.8% and 7.5% had irregular bleeding; 31.4% and 74.3% had normal bleeding; 3.6% and 0.5% had frequent bleeding; 3.6% and 0.5% had prolonged bleeding (according to WHO criteria). Regardless of bleeding pattern, discontinuations due to bleeding pattern alterations were uncommon: occurring in 7 women and 1 woman in the LNG-IUS13.5mg and COC groups, respectively.

CONCLUSION: **Even in the context of a clinical trial, the efficacy of COC was apparently reduced by non-compliance.** In contrast, the efficacy of LNG-IUS13.5mg is not dependent on user compliance. Women using LNG-IUS13.5mg generally experienced shorter, less frequent bleeding over time, and were more likely to experience amenorrhea and infrequent bleeding than COC users.



Pharma AG, Berlin,
profiles associated
0 mg ethinyl estrac



any, NJ.

(nt) levonorgestrel
oral contraceptive

A MULTICENTER, RANDOMIZED PHASE III STUDY COMPARING A 13.5 MG LEVONORGESTREL INTRAUTERINE CONTRACEPTIVE SYSTEM WITH A COMBINED ORAL CONTRACEPTIVE: ANALYSIS OF USER SATISFACTION AND SAFETY.

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OBJECTIVE: To compare use of the LNG-IUS13.5mg intrauterine contraceptive system (LNG-IUS13.5mg) with use of the estradiol/3 mg drospirenone (COC).

(AEs) with use of the estradiol/3 mg drospirenone (COC).

DESIGN: Phase III study at 4 sites.

MATERIALS AND METHOD: Women requesting contraception, were randomized to the LNG-IUS13.5mg or COC for 18 months.

(aged 18-29 years, requesting

days), requesting

contraception, were randomized to the LNG-IUS13.5mg or COC for 18 months.

COC for 18 months

Primary outcome: user satisfaction.

RESULTS: The full analysis set included **279 women randomized to LNGIUS13.5mg** for whom placement was attempted (successful in 279), and **281 women randomized to COC** who took R1 pill. In the LNG-IUS13.5mg and COC groups, respectively, the mean age was 23.7 and 23.9 years, and **77.4% and 73.3% were nulliparous**. Among LNG-IUS13.5mg and COC users, respectively, 36.6% and 15.3% reported study drug-related AEs. LNGIUS13.5mg users were more likely than COC users to report **acne (9.0% vs 0.4%), dysmenorrhea (8.2% vs 1.1%), ovarian cyst (5.7% vs 0.0%), and abdominal pain (5.0% vs 0.0%)**. There were 3 drug-related serious AEs in the **LNG-IUS13.5mg group; ectopic pregnancy, spontaneous abortion, and ovarian cyst**. (There were 2 spontaneous abortions in the COC group; these were not considered drug-related). 9.7% and 0.7% of LNG-IUS13.5mg and COC users, respectively, reported AEs related to protocol-required procedures; mainly insertion-related discomfort. **At Month 18/end of study (EOS), 268 and 251 women** in the LNG-IUS13.5mg and COC groups, respectively, completed a **general satisfaction questionnaire; 82.1% and 81.7%, respectively, reported they were either 'very satisfied' or 'satisfied'** with study treatment, with 58.6% and 46.6%, respectively, reporting they were 'very satisfied'. At Month 18/EOS, in the LNG-IUS13.5mg and COC groups, 263 and 250 women, respectively, completed a satisfaction and bleeding questionnaire; 91.3% and 92.8% rated administration of study treatment as 'acceptable with/without some inconvenience/discomfort'; 63.1% and 70.0% reported being 'very/somewhat satisfied' with their bleeding pattern; and **66.2% and 48.8% reported that, given the choice, they would continue using study treatment** after the study.

CONCLUSION: LNG-IUS13.5mg and a COC were **both associated with high user satisfaction and were well tolerated**. Although the LNGIUS13.5mg group reported a higher incidence of AEs, they were more likely to prefer to continue their method after the study.



A MULTICENTER, OPEN-LABEL, SINGLE-ARM STUDY EXPLORING THE SAFETY OF A NEW 13.5 MG TOTAL DOSE LEVONORGESTREL INTRAUTERINE CONTRACEPTIVE SYSTEM IN POSTMENARCHEAL ADOLESCENTS.

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HealthCare, Newbury, United Kingdom; ^eBayer HealthCare, Whippany, NJ; ^fSexual Health Clinic, V&A



}; ^dBayer

3-IUS13.5mg; **Skyla**

OBJECTIVE: To assess the safety profile of the 13.5 mg total content levonorgestrel intrauterine con
in the US, **Jaydess** elsewhere) over **1 year of use in postmenarcheal adolescents aged <18 years**.

DESIGN: Phase III study conducted at **36 centers in Europe**.

Primary outcome: incidence of any treatment-emergent adverse event (TEAE).

MATERIALS AND METHODS: Nulliparous and parous women, **aged 12-17 years**, with regular menstrual cycles (21-35 days), requesting
contraception were recruited.

RESULTS: Of the 343 subjects enrolled, 39 were excluded at screening, and up to 2 attempts at LNG-IUS13.5mg placement were made for 304
subjects (full analysis set [FAS]); **placement was successful in 303/304**. In the FAS, the mean age was 16.2 years, mean BMI was 22.1 kg/m²,
and **97.7% were nulliparous**. At screening, 51.6%, 22.7%, and 22.7% of subjects were using oral contraceptives, barrier methods, and no
contraception, respectively. Overall, 82.6%, 41.8%, and 20.7% of subjects reported any TEAEs, drug-related TEAEs, and study procedure-
related TEAEs, respectively. The most common drug-related TEAEs by MedDRA preferred term were pelvic pain (14.8%) and dysmenorrhea
(12.2%). All other drug-related TEAEs were reported by <7% of subjects. **There were no cases of pelvic inflammatory disease, pregnancy, or
uterine perforation. 10 (3.3%) device expulsions occurred (1 complete and 9 partial [confirmed by ultrasound])**. There was **no clinically
relevant change in mean body weight** over time. In total, 253 (83.2%) completed the 1-year study; 42 subjects (13.8%) discontinued due to
TEAEs. TEAEs that most frequently led to discontinuation were: pelvic pain (3.9%), device expulsion (3.3%), acne (1.6%), and dysmenorrhea
(1.6%). 2 subjects (0.7%) discontinued due to treatment-emergent SAEs (endometritis and pelvic pain).

CONCLUSION: **The safety profile of LNG-IUS13.5mg in this adolescent cohort was consistent with that reported in adults**. No new or
unexpected safety concerns were associated with LNG-IUS13.5mg. The continuation rate was highly favorable for an adolescent population.

A PHASE III SINGLE-ARM STUDY OF A NEW 13.5 MG LEVONORGESTREL INTRAUTERINE CONTRACEPTIVE SYSTEM IN **POSTMENARCHEAL ADOLESCENTS**: AN EVALUATION OF EFFICACY, BLEEDING, USER SATISFACTION, AND PLACEMENT

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^a Bayer HealthCare, Newbury, United Kingdom; ^e Bayer HealthCare, Whippany, NJ; ^f Sexual Health Clinic, Vaestoliitto, Finla



OBJECTIVE: To evaluate the efficacy, bleeding profile and user satisfaction associated with the 13.5 mg total content levonorgestrel intrauterine contraceptive system (LNG-IUS13.5mg; Skyla in the US, Jaydess elsewhere) in **postmenarcheal adolescents**, and to evaluate the placement of LNGIUS13.5mg in this group. Safety (primary outcome) data are presented in another abstract.

DESIGN: A 1-year Phase III study conducted at **36 centers in Europe** (with an option to continue use for 2 more years).

MATERIALS AND METHODS: **Nulliparous and parous women, aged 12-17 years**, with regular menstrual cycles (21-35 days), requesting contraception were recruited.

RESULTS: Of the 343 subjects enrolled, 39 were excluded at screening; LNG-IUS13.5mg placement was attempted in the remaining **304 subjects** (the full analysis set). The mean age was 16.2 years, mean BMI was 22.1 kg/m², and 97.7% were nulliparous. **At screening, 51.6% of subjects used oral contraceptives, 22.7% used barrier methods, and 22.7% used no contraception.** The 1-year Pearl Index (PI) was 0.00. However, only 72% of the total exposure was relevant to the PI calculation because subjects were counseled to use barrier methods to prevent sexually transmitted infections. Placement was successful in 303/304 subjects. Investigators rated 94.4% of successful placements as 'easy'. **Pain on placement was rated as 'none', 'mild', 'moderate', and 'severe', respectively, by 20.5%, 34.3%, 34.3%, and 10.9% of subjects.** Between the 1st and 13th (final) 28-day reference intervals (RIs), **the mean number of combined bleeding and spotting days decreased from 16.9 to 6.5.** The mean number of bleeding/spotting episodes per RI remained relatively constant over time (range: 0.8-1.4). However, the number of subjects contributing data to bleeding analyses decreased from 141 in RI 1 to 36 in RI 13. At 1 year, 83.9% of subjects

CONCLUSION: In this adolescent population, LNG-IUS13.5mg was highly effective, associated with high user satisfaction, and had a **similar bleeding profile to that observed in the adult population.** Most placements were rated as 'easy', and most subjects experienced no more than 'mild' pain on placement.

A 12-MONTH MULTICENTER, RANDOMIZED PHASE III STUDY COMPARING A 13.5 MG LEVONORGESTREL INTRAUTERINE CONTRACEPTIVE SYSTEM WITH THE ETONOGESTREL SUBDERMAL CONTRACEPTIVE IMPLANT IN WOMEN AGED 18–35 YEARS.

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OBJECTIVE: To compare 12-month rates of discontinuation (primary outcome), and other outcomes) associated with the use of a new 13.5 mg (total content) levonorgestrel intrauterine system (LNG-IUS, Mirena) and the etonogestrel subdermal contraceptive implant (ENG implant, Nexplanon).

DESIGN: A randomized, 2-arm, open-label Phase III study conducted in Australia, Finland, France, Norway, Sweden and the UK.

MATERIALS AND METHODS: Healthy nulliparous and parous women aged 18–35 years with regular menstrual cycles (21–35 days), requiring contraception, were randomized to use LNG-IUS 13.5 mg or ENG implant for 12 months.

RESULTS: In total, 766 women were randomized to use either LNG-IUS 13.5 mg (385) or the ENG implant (381). In the LNG-IUS 13.5 mg and ENG implant groups, respectively, the mean age was 24.8 years and 25.0 years, the mean BMI was 23.6 kg/m² and 24.3 kg/m², and 76.2% and 72.2% were nulliparous. Within 12 months, 19.6 % of LNG-IUS 13.5 mg users and 26.8% of implant users prematurely discontinued treatment; this -7.2% difference in favor of LNG-IUS 13.5 mg was statistically significant (95% CI: -13.2%, -1.2%). Premature discontinuation rates owing to altered bleeding pattern were 4.2% (LNG-IUS 13.5 mg) and 11.5% (ENG implant).

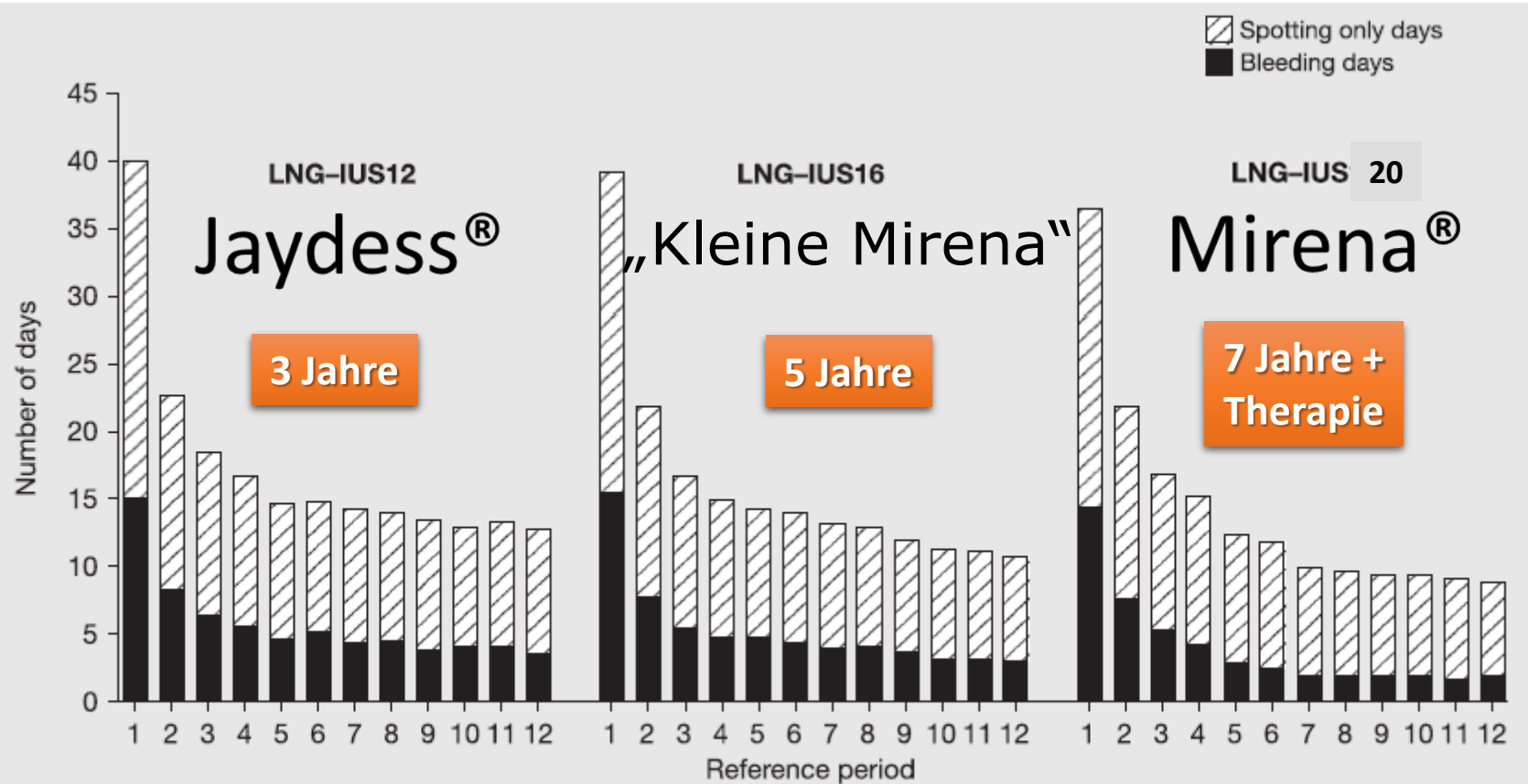
Depending on time point (month 6, month 12, end of study), overall user satisfaction rates ranged from 80.2% to 86.5% (LNG-IUS 13.5 mg) and from 66.1% to 75.9% (ENG implant). Among LNG-IUS 13.5 mg users, the most frequently reported AEs were dysmenorrhea (33.5%), uterine spasms (16.2%), and procedural pain (13.6%). The most frequent AEs in the ENG implant group were acne (15.5%), headache (12.3%), and dysmenorrhea (12.3%). No unexpected safety events were reported. Three pregnancies were reported, all in the LNG-IUS 13.5 mg group; however the study was not powered to accurately determine pearl indices.

CONCLUSION: The primary outcome was reached; the 12-month discontinuation rate in the LNG-IUS 13.5 mg group was significantly lower than in the ENG implant group. Additionally, compared with the ENG implant, the LNG-IUS 13.5 mg was associated with a lower discontinuation rate owing to altered bleeding pattern. Greater user satisfaction was seen with LNG-IUS 13.5 mg than with the implant. Both the LNG-IUS 13.5 mg and the ENG implant were well tolerated.



A randomized, phase II study describing the efficacy, bleeding

FIGURE 1



Mean number of bleeding or spotting days per 90-day reference period during the 3 years of the intrauterine system use (reference periods 1–12). Drop-outs were not accounted for in this analysis; the results are based on subjects participating during the respective reference period. The drop-out rates (for any reason) were 27.2%, 29.0%, and 28.3% in the LNG-IUS12, LNG-IUS16, and Mirena arms, respectively. It is possible that subjects dropping out as a result of changes in bleeding patterns may have influenced these results. LNG-IUS = levonorgestrel intrauterine system.

INTRODUCING LILETTA



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A Study of a Levonorgestrel-Releasing Intrauterine System for Long-Term, Reversible Contraception

This study is ongoing, but not recruiting participants.

Sponsor:

Medicines360

Information provided by (Responsible Party):

Medicines360

ClinicalTrials.gov Identifier:

NCT00995150

First received: October 13, 2009

Last updated: January 21, 2015

Last verified: January 2015

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Original research article

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

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Received 13 March 2015; revised 15 April 2015; accepted 17 April 2015

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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