Pharmacokinetics of two low-dose levonorgestrel-releasing intrauterine systems and effects on ovulation rate and cervical function: pooled analyses of phase II and III studies

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Objective: To assess the pharmacokinetics and pharmacodynamics of levonorgestrel intrauterine system (LNG-IUS) 13.5 mg and LNG-IUS 19.5 mg (total content).
Design: Pooled pharmacokinetic and pharmacodynamic analyses of phase II and III studies.
Setting: Randomized, open-label, multicenter studies.
Patient(s): Nulliparous and parous women.
Intervention(s): Levonorgestrel intrauterine system 13.5 mg, LNG-IUS 19.5 mg, or LNG-IUS 20 μg/24 h (total content 52 mg).
Main Outcome Measure(s): Pharmacokinetics of LNG, ovulation rate, cervical function, and endometrium effects.
Result(s): The in vivo LNG release rate of LNG-IUS 13.5 mg was approximately 14 μg/24 h after 24 days, declining progressively to 5 μg/24 h after 3 years. The average LNG serum concentration over 3 years of use was 74.3 ng/L, 114 ng/L, and 218 ng/L for LNG-IUS 13.5 mg, LNG-IUS 19.5 mg, and LNG-IUS 20 μg/24 h, respectively. All treatments showed very similar progestogenic effects on cervical mucus, with low and similar cervical scores throughout treatment. Ovulation was observed in the majority of women in all groups where assessment was possible, although there was a lower incidence of anovulation with LNG-IUS 13.5 mg and LNG-IUS 19.5 mg compared with LNG-IUS 20 μg/24 h. The progestogenic effect on the endometrium was marked in all three LNG-IUS groups.
Conclusion(s): Levonorgestrel intrauterine system 13.5 mg and LNG-IUS 19.5 mg result in a lower systemic exposure to LNG, lower incidence of anovulation, and similar progestin impact on the endometrium and cervical function compared with LNG-IUS 20 μg/24 h. (Fertil Steril® 2014;101:1656–62. ©2014 by American Society for Reproductive Medicine.)
Key Words: Low-dose levonorgestrel intrauterine system, pharmacodynamics, pharmacokinetics

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The currently available levonorgestrel (LNG) intrauterine system (IUS), LNG-IUS 20 μg/24 h (total content 52mg), known as Mirena (Bayer Healthcare Pharmaceuticals Inc.), is a highly effective method of contraception and is suitable for use in a wide range of women. LNG-IUS 20 μg/24 h has mainly local progestogenic effects in the uterine cavity, including alteration of the endometrium, inhibition of sperm transport,

capacitation, and survival, and thickening of the cervical mucus (1). LNG-IUS 20 μg/24 h may also affect ovulation in particular during the first year; thereafter, most cycles are ovulatory, and the incidence of ovulatory cycles with LNG-IUS 20 μg/24 h and with the copper intrauterine device (Multiload Cu250, Multilan AG) is the same (85%) (2, 3). In general, the anovulatory cycles (5%–15% of treatment cycles) correlate with higher levels of LNG (3, 4).

With the LNG-IUS, LNG is released directly into the uterine cavity, resulting in very low systemic exposure to progestogen (1), which is not the case with other LNG-containing contraceptives, such as implants, combined oral contraceptives (COCs), and progestin-only oral contraceptives (5–7). Nevertheless, side effects related to systemic exposure to progestogen have been reported to occur in some LNG-IUS 20 μg/24 h users (8).

Bayer HealthCare has developed two experimental lower-dose LNG intrauterine systems, LNG-IUS 13.5 mg (total content), also known as Jaydess, and LNG-IUS 19.5 mg (total content), which have been evaluated in two randomized, open-label, multicenter trials in nulliparous and parous women. In a phase II study, both LNG-IUS 13.5 mg and LNG-IUS 19.5 mg demonstrated good contraceptive efficacy (3-year Pearl Index: LNG-IUS 13.5 mg, 0.17; LNG-IUS 19.5 mg, 0.82), which was similar to that of LNG-IUS 20 μg/24 h (3-year Pearl Index: 0.00). However, this study was not powered accurately to determine the Pearl Indices for these products. The bleeding profiles of LNG-IUS 13.5 mg and LNG-IUS 19.5 mg were also similar to that of LNG-IUS 20 μg/24 h; however, the total number of bleeding and spotting days increased with decreasing LNG dose (9). In a phase III study, LNG-IUS 13.5 mg and LNG-IUS 19.5 mg again demonstrated excellent contraceptive efficacy (3-year Pearl Index: LNG-IUS 13.5 mg, 0.33; LNG-IUS 19.5 mg, 0.31), with similar bleeding profiles, as well as high continuation and user satisfaction rates (10).

The principal objectives of the analyses included in this study were to assess the pharmacokinetics (PK) and pharmacodynamics (PD) of LNG-IUS 13.5 mg and LNG-IUS 19.5 mg using pooled data from the phase II and III studies.

MATERIALS AND METHODS

The phase II study (clinicaltrials.gov: NCT00185380) included 742 women randomized to 3 years' treatment with LNG-IUS 13.5 mg, LNG-IUS 19.5 mg, or LNG-IUS 20 μg/24 h (9). The subsequent phase III study (clinicaltrials.gov: NCT00528112) included 2,885 women randomized to 3 years' treatment with either LNG-IUS 13.5 mg or LNG-IUS 19.5 mg (10). In both studies, randomization was set up centrally by the study statistician using a computerized randomization program and was balanced for study sites. Randomization blocks were used with an allocation ratio of 1:1:1 and 1:1 in the phase II and III study, respectively. Sealed randomization envelopes (phase II study) and numbered randomization cards and a randomization list (phase III study) were prepared for each study site and used in sequential ascending order to inform the investigator of which treatment each participant was to be allocated. Although women were blinded to treatment allocation, it was not possible to blind investigators because LNG-IUS 20 μg/24 h could be distinguished by its larger dimensions and because of the discernible differences in the length of the hormone reservoirs of LNG-IUS 13.5 mg and LNG-IUS 19.5 mg. The design and conduct of these studies have been reported previously (9, 10).

The full analysis set in the phase II study, which was used for all efficacy and safety analyses, was based on all randomized subjects who had a successful LNG-IUS placement (LNG-IUS 13.5 mg: n = 239; LNG-IUS 19.5 mg: n = 245; LNG-IUS 20 μg/24 h: n = 254). All randomized subjects in the phase III study in whom a placement was at least attempted were analyzed according to the treatment actually received and were included in the full analysis set. One woman was randomized in the phase III study, but no placement was attempted; this woman was excluded from the full analysis set of 2,884 women (LNG-IUS 13.5 mg: n = 1,432 women; LNG-IUS 19.5 mg: n = 1,452 women). Overall, 35.6% of women across both studies were nulliparous. From the full analysis set in each study, subsets of women were enrolled for detailed PK and PD analyses. In total, from the two studies, 60 women were enrolled for detailed PK analyses, 92 women were enrolled for assessment of ovulation rate and cervical function, and 150 women were enrolled for endometrial histologic analyses. The protocol and its amendments were reviewed and approved by each study site's independent ethics committee or institutional review board.

Calculation of in vivo LNG Release Rates

A model developed in NONMEM together with software R was used to calculate the release rates of LNG from LNG-IUS 13.5 mg using ex vivo residual content data from the phase III study. The dataset used for the model development included 763 LNG-IUS 13.5 mg residual content measurements obtained at different time points over 3 years from subjects who either discontinued or completed the study.

Owing to the rapid changes in the release rates within the first months for the new LNG-IUS, release rates at several time points were provided to characterize the release of LNG-IUS 13.5 mg. Release rates were provided for day 25 (i.e., 24 days after insertion), 60 days after insertion, and at the end of the 3-year treatment period. In addition, the average release rate over the 3 years of treatment was calculated.

In vivo LNG release rates for LNG-IUS 20 μg/24 h have been reported (11). Release rates for LNG-IUS 20 μg/24 h were calculated using in vitro data based on an in vitro–in vivo correlation model. An initial in vivo release rate for LNG-IUS 20 μg/24 h was calculated. In addition, release rates were provided at the end of treatment and on average over 5 years of treatment (11).

Drug Concentration Determination for Population PK Evaluation

All subjects in the phase III study provided at least one blood sample over the 3-year treatment period for determination of LNG and sex hormone–binding globulin (SHBG) concentrations for population PK modeling. To achieve an

approximately equal distribution of blood samples over the whole treatment period, the time point at which each sample was taken was randomized. Additionally, a blood sample was taken from every subject who prematurely discontinued the study before removal of the IUS.

Concentration data collected during the phase III study were assessed using nonlinear mixed-effects models. Mixed-effect models, or population-type PK models, describe the relationship between dose and time and variables, such as drug serum concentrations. Both fixed (measurable factors, e.g. dose, time, age) and random (nonmeasurable factors, e.g. model misspecification) effects are involved in this relationship. A population PK compartmental model was developed, using the serum concentration of LNG as the dependent variable.

On the basis of this model, individual, total, and unbound LNG serum concentrations for LNG-IUS 13.5 mg and LNG-IUS 19.5 mg were estimated after 1, 7, and 30 days, 3 months, and 1, 2, and 3 years. The model describes the release of LNG from LNG-IUS 13.5 mg and LNG-IUS 19.5 mg and the resultant LNG serum concentration, taking into account the interaction with SHBG. The inclusion of SHBG was required to describe the PK of LNG, because the elimination of LNG depends on SHBG. Unbound LNG serum concentrations for LNG-IUS 13.5 mg and LNG-IUS 19.5 mg were calculated using SHBG and total LNG serum concentrations.

Determination of Drug Concentration Based on Noncompartmental Analysis of Pooled Subgroup Data

Serum levels of LNG and SHBG were investigated according to frequent blood sampling at the start of study treatment. Only subjects with PK data available up to 3 years in the two studies and on entering the study, who had not switched from another form of hormonal contraception within the month before initiating study treatment, were included in this pooled analysis.

In the phase II study, blood samples were taken at baseline (before LNG placement) and on days 1, 3, 7, and 14, as well as at every regular visit (i.e., 1, 6, 12, 18, 24, 30, and 36 months after insertion) and at the end of study treatment before IUS removal. Similarly, in the phase III study, blood samples were taken at baseline (before LNG placement) and on days 1, 3, 7, and 14, as well as at every regular visit (i.e., 3, 6, 9, 12, 18, 24, 30, and 36 months after insertion) and before IUS removal.

For the assessment of LNG serum levels, the PK parameters maximum observed serum concentration (C_{max}), time to reach maximum observed serum concentration (t_{max}), observed serum concentration at 3 years after placement (C_{3y}), area under the curve [AUC(0-3y)], and average steady-state serum concentration (C_{av}) were calculated.

Determination of Serum Estradiol and Progesterone

A blood sample was taken twice a week for 6 weeks in the second half of each year of study (years 1, 2, and 3) to determine serum estradiol and progesterone concentrations. Sampling for serum concentration levels of LNG and SHBG were also carried out during these periods.

Pooled Analyses of Ovulation Rate and Cervical Function

All subjects with serum progesterone values $\geq$2.5 ng/mL were assessed as having evidence of ovulation (based on listings of individual progesterone values). In addition, results were confirmed using a slightly higher progesterone threshold of 3.0 ng/mL (phase III study data only)—this threshold value is in alignment with the published value used to observe ovulation (12, 13).

Cervical function was studied on the same days as ovulation rate using the Insler scoring system. The Insler score is a composite score incorporating subscores (on a scale of 0–3) for amount of cervical mucus, spinnbarkeit, ferning, and appearance of the cervix (Supplemental Table 1, available online) (14). The total cervical score (between 0 and 12) was defined as the sum of the subscores.

Pooled Analysis of Effects on the Endometrium

Endometrial histology was studied through the review of annual endometrial biopsies (at baseline and after 1, 2, and 3 years of treatment) by a pathologist who was blinded as to which treatment group each subject was in. The endometrium was evaluated for descriptive classification and estrogen and progesterone effects, as well as for safety. Estrogenic and progestogenic effects were categorized as 0, 1, 2, or 3, which corresponded to none, weak, moderate, and marked, respectively.

RESULTS

In vivo LNG Release Rates

The in vivo LNG release rate of LNG-IUS 13.5 mg was approximately 14 μg/24 h after 24 days, which decreased to approximately 10 μg/24 h after 60 days. It then declined progressively to 5 μg/24 h after 3 years. The average in vivo LNG release rate of LNG-IUS 13.5 mg was approximately 6 μg/24 h over the period of 3 years. In vivo release rates for LNG-IUS 20 μg/24 h declined at a more stable rate over time compared with LNG-IUS 13.5 mg. As previously described, the initial in vivo release rate for LNG-IUS 20 μg/24 h is 20 μg/24 h and is reduced to 10 μg/24 h after 5 years (11). Over a period of 5 years the average in vivo LNG release rate of LNG-IUS 20 μg/24 h is approximately 14 μg/24 h (11).

Drug Concentration Determination Based on a Population PK Approach Using All Subjects of the Phase III Study

On the basis of data from 2,547 women in the phase III study, estimated total LNG serum concentrations for LNG-IUS 13.5 mg and LNG-IUS 19.5 mg were 116 ng/L (coefficient of variation [CV], 18.1%), and 140 ng/L (CV, 19.0%), respectively, 1 day after placement of the devices. After 1, 2, and 3 years, the mean total concentration declined to 71.0 ng/L (CV, 27.3%),

64.3 ng/L (CV, 27.6%), and 58.6 ng/L (CV, 29.4%), respectively, for LNG-IUS 13.5 mg, and to 109.0 ng/L (CV, 28.3%), 100.0 ng/L (CV, 28.1%), and 96.8 ng/L (CV, 27.7%), respectively, for LNG-IUS 19.5 mg (Supplemental Table 2).

Estimated unbound LNG serum concentrations for LNG-IUS 13.5 mg and LNG-IUS 19.5 mg were 1.67 ng/L (CV, 11.1%) and 2.03 ng/L (CV, 12.1%), respectively, 1 day after placement of the devices. The estimated concentration of unbound LNG at 1, 2, and 3 years was 1.05 ng/L (CV, 21.3%), 0.947 ng/L (CV, 21.4%), and 0.871 ng/L (CV, 23.1%), respectively, for LNG-IUS13.5 mg, and 1.64 ng/L (CV, 22.8%), 1.50 ng/L (CV, 22.8%), and 1.45 ng/L (CV, 22.6%), respectively, for LNG-IUS 19.5 mg (Supplemental Table 2).

Determination of Drug Concentration Based on Noncompartmental Analysis of Pooled Subgroup Data

After placement of LNG-IUS 13.5 mg, a geometric mean LNG C_{max} value of 148 ng/L (CV, 43.4%) was reached after 8 days. After placement of LNG-IUS 19.5 mg, the corresponding value was 214 ng/L (CV, 60.8%) after 11 days (Table 1). The mean C_{max} value of LNG for LNG-IUS 20 μg/24 h was 342 ng/L (CV, 43.1%) after 14 days and was approximately 2.3 times higher than the value for LNG-IUS 13.5 mg. The average concentration over the 3-year period of use was 74.3 ng/L (CV, 35.8%), 114.0 ng/L (52.9%), and 218.0 ng/L (35.2%) for LNG-IUS 13.5 mg, LNG-IUS 19.5 mg, and LNG-IUS 20 μg/24 h, respectively.

Levonorgestrel mean concentration levels in serum declined gradually over time to geometric mean values of 68.3 ng/L (CV, 34.1%), 95.1 ng/L (CV, 60.9%), and 165.0 ng/L (CV, 40.5%) at 36 months after placement of LNG-IUS 13.5 mg, LNG-IUS 19.5 mg, and LNG-IUS 20 μg/24 h, respectively (Fig. 1A).

Geometric mean concentration levels of SHBG in serum at baseline were 56.9 nmol/L (CV, 44.4%) for LNG-IUS 13.5 mg, 70.5 nmol/L (CV, 63.4%) for LNG-IUS 19.5 mg, and 54.3 nmol/L (CV, 41.7%) for LNG-IUS 20 μg/24 h. After an initial decline in the first week, SHBG serum levels showed almost stable, plateau-like values over the 36-month period after placement of LNG-IUS 13.5 mg. Serum levels of SHBG also declined in the first week after placement of LNG-IUS 19.5 mg and LNG-IUS 20 μg/24 h. Thereafter, SHBG serum levels showed greater fluctuation over time (Fig. 1B).

Determination of Serum Estradiol

Mean average estradiol values showed high variability, with no clear tendency for an increase or decrease over time (Supplemental Table 3). Mean C_{av} values varied between 93.3 ng/L (standard deviation [SD], 28.1 ng/L; LNG-IUS 19.5 mg, year 2 in the phase II study) and 141.6 ng/L (SD, 83.8 ng/L; LNG-IUS 20 μg/24 h, year 3 in the phase II study). No difference between the treatments in the two studies was observed.

Pooled Analysis of Ovulation Rates

On the basis of serum progesterone values $\geq$2.5 ng/mL, evidence of ovulation was observed in most women at all examinations in the LNG-IUS 13.5 mg group (n = 35), although one woman in year 1 and one woman in year 2 showed no evidence of ovulation (Table 2). In the LNG-IUS 19.5 mg group (n = 26), ovulation was observed in most women at all examinations, although three women showed no evidence of ovulation in year 1 and one woman (who ovulated in year 1) showed no evidence of ovulation in year 2. Additionally, in the LNG-IUS 20 μg/24 h group (n = 17), ovulation was observed in most women at all examinations; however, four women in year 1, two women in year 2, and one woman in year 3 showed no evidence of ovulation. The same analysis performed using a serum progesterone threshold value >3.0 ng/mL yielded identical results (phase III study only: data not shown).

Pooled Analysis of Cervical Function

Across both studies, all treatments showed very similar progestogenic effects on the cervical mucus, with low and similar cervical scores over the whole treatment period, indicating cervical mucus that is impenetrable by sperm (Fig. 2). Mean total cervical scores for LNG-IUS 13.5 mg, LNG-IUS 19.5 mg, and LNG-IUS 20 μg/24 h over 3 years were 3.4, 3.0, and 3.5, respectively.

Pooled Analysis of Effects on the Endometrium

Histologic evaluation of the endometrium at years 1, 2, and 3 showed normal findings for all women in whom assessment was possible (on average, 4% of women were missing at

TABLE 1

Mean PK parameters of LNG observed after placement of LNG-IUS 13.5 mg, LNG-IUS 19.5 mg, and LNG-IUS 20 μg/24 h: pooled analysis of subsets of patients from phase II and III studies included in a noncompartmental analysis.

Parameter	LNG-IUS 13.5 mg (n = 15)	LNG-IUS 19.5 mg (n = 13)	LNG-IUS 20 μg/24 h (n = 12)[a]
[AUC(0–3y)], μg•d/L	81.4 (35.7)	125.0 (52.4)	238 (35.1)
C_{max}, ng/L	148.0 (43.4)	214.0 (60.8)	342 (43.1)
t_{max}, days	8 (1–379)	11 (3–364)	14 (3–927)
C_{av}, ng/L	74.3 (35.8)	114 (52.9)	218 (35.2)
C_{3y}, ng/L	68.3 (34.1)	95.1 (60.9)	165 (40.5)

Note: For all pharmacokinetic parameters the geometric mean (geometric coefficient of variation, %) is given, except for t_{max}, where the median (range) is provided. [AUC(0–3y)] = area under the drug serum concentration–time curve from time 0 to the last data point >LLOQ; C_{max} = maximum observed serum concentration; t_{max}, time to reach C_{max}; C_{av} = average steady state serum concentration [AUC(0–3y)] divided by the time interval from insertion until the last measured serum concentration; C_{3y} = observed serum concentration at 3 years after placement; LLOQ = lower limit of quantification.

[a] Data from phase II study only.

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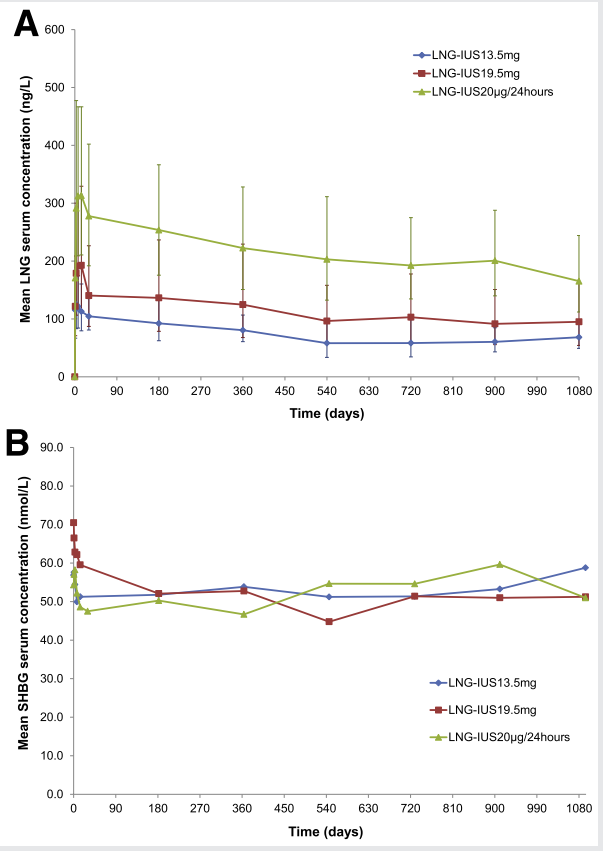
FIGURE 1



(A) Serum LNG (ng/L). (B) Serum SHBG (nmol/L). The geometric mean concentrations of LNG (ng/L) and SHBG (nmol/L) in serum by treatment: pooled analyses from phase II and III studies.

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each examination). Abnormalities were found at baseline only (two women in the LNG-IUS 13.5 mg group and two women in the LNG-IUS 19.5 mg group). As expected, there was a decrease in estrogen effects and an increase in progestin effects on the endometrium over time (data not shown). Histologic classification of the endometrium indicated that the endometrium was proliferative in the majority of women classified at baseline (Supplemental Table 4). Conversely, at years 1, 2, and 3, the endometrium was secretory in the majority of women in whom endometrial histology was classified, irrespective of treatment assignment (Supplemental Table 4). The progestin effect on the endometrium was marked in all treatment groups at all time points assessed (99.4% of biopsies in all treatment groups combined [359 of 361 biopsies]), indicating a high degree of endometrial suppression.

DISCUSSION

These pooled analyses of subjects from the phase II and III studies show that the two low-dose LNG-IUSs, LNG-IUS 13.5 mg and LNG-IUS 19.5 mg, result in a lower systemic exposure to LNG, a lower incidence of anovulation, and similar effects on the endometrium and cervical function compared with LNG-IUS 20 μg/24 h.

After placement, LNG is released from the IUS into the uterine cavity without delay, as evidenced by serum concentration measurements (Table 1). According to the t_{max} range for LNG-IUS 13.5 mg (1–379 days), highest concentrations were already observed at day 1 in some subjects. It should be noted that the large range of individual t_{max} values indicates a high variability of this parameter and that there were no differences between the LNG-IUSs. Individual concentration–time profiles overlap strongly, despite the large range of t_{max} values. The concentration–time profile of the geometric mean curve is generally representative for the individual curves, signifying that there is a rapid increase in LNG serum concentration. The numerically high t_{max} values are due to SHBG-induced peaks in the plateau-like phase but do not reflect the overall concentration–time profile. A notable difference between LNG-IUS 20 μg/24 h and LNG-IUS 13.5 mg or LNG-IUS 19.5 mg is that the ends of the drug-containing elastomer core of LNG-IUS 13.5 mg and LNG-IUS 19.5 mg are open, leading to a faster initial release after placement (as evidenced by in vivo LNG release rate data for LNG-IUS 13.5 mg). Thereafter, LNG release becomes controlled more by the membrane and less by the open ends, which results in a decline in the LNG release rate and a

TABLE 2

Ovulation by treatment and year in evaluable subjects: pooled analysis from phase II and III studies (ovulation indicated by serum progesterone values ≥2.5 ng/mL).[a]

Year	Parameter	LNG-IUS 13.5 mg	LNG-IUS 19.5 mg	LNG-IUS 20 μg/24 h	Total
1	No. of subjects	35 (100)	26 (100)	17 (100)	78 (100.0)
	No ovulation	1 (3.0)	3 (11.5)	4 (23.5)	8 (10)
	Ovulation	34 (97.0)	23 (88.5)	13 (76.5)	70 (90)
2	No. of subjects	27 (100.0)	20 (100.0)	13 (100.0)	60 (100.0)
	No ovulation	1 (4.0)	1 (5.0)	2 (15)	4 (7.0)
	Ovulation	26 (96)	19 (95.0)	11 (85)	56 (93)
3	No. of subjects	26 (100.0)	16 (100.0)	11 (100.0)	53 (100.0)
	No ovulation	0	0	1 (9.0)	1 (2.0)
	Ovulation	26 (100.0)	16 (100.0)	10 (91.0)	52 (98.0)

Note: Values are number (percentage). Only subjects with evaluable specimens for ovarian function were included in these pooled analyses.
[a] A value of 2.5 ng/mL has been demonstrated by internal modeling studies to indicate ovulation.

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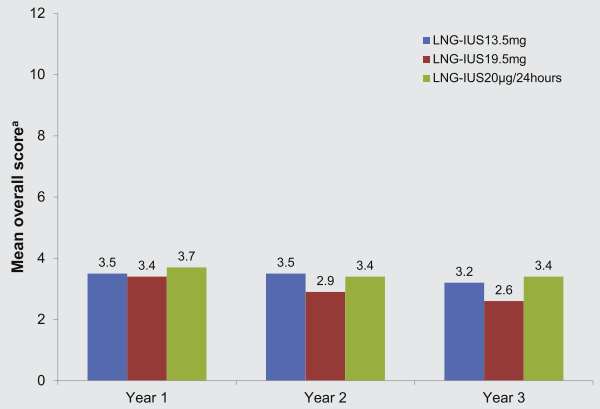
FIGURE 2



Cervical function (Insler score) by treatment and year in pooled phase II and III studies. Only subjects with evaluable specimens for cervical function were included in these pooled analyses. [a]Mean overall score was defined as the sum of the subscores and is a number between 0 and 12. The total number of subjects per each treatment arm in whom cervical function was assessed was as follows: LNG-IUS 13.5 mg: year 1 (n = 35), year 2 (n = 27), year 3 (n = 25); LNG-IUS 19.5 mg: year 1 (n = 27), year 2 (n = 21), year 3 (n = 15); LNG-IUS 20 µg/24 h: year 1 (n = 17), year 2 (n = 13), year 3 (n = 11).

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gradual and continuous release over time. Even though differences in the release rates of the LNG-IUSs were evident, the shape of the PK profile is similar for each device, which suggests that high initial release rates do not result in high systemic exposure during these early days after placement.

Despite the early maximum LNG concentrations observed with LNG-IUS 13.5 mg and LNG-IUS 19.5 mg, the use of these two low-dose LNG-IUSs results in a lower systemic exposure to LNG over time compared with LNG-IUS 20 µg/24 h (Fig. 1A). An LNG serum concentration of 194 pg/mL (146–266 pg/mL) 12 months after placement of LNG-IUS 20 µg/24 h has previously been reported (15), which is higher than the estimated total LNG serum concentration for LNG-IUS 13.5 mg at 12 months during the population PK modeling (Supplemental Table 2). Serum LNG concentrations associated with other LNG-containing contraceptives have also been reported. For example, after repeated administration of a low-dose COC (100 µg LNG and 20 µg ethinylestradiol (EE)), mean maximum LNG serum concentrations of 4,530 ng/L were observed (16). This value is more than 25 times higher than the estimated maximum concentration observed with LNG-IUS 13.5 mg (162 ng/L, 7 days after placement) (Supplemental Table 2). Because the protein binding of LNG is higher for a COC (because of the induced SHBG concentration), comparison of unbound LNG concentrations between LNG-IUS 13.5 mg and the COC is more appropriate. The fraction of unbound LNG for the low dose COC containing 100 µg LNG and 20 µg EE during steady state is 0.8%, resulting in a mean maximum concentration of unbound LNG of 36.2 ng/L (16), which is nevertheless 15 times higher than the estimated unbound LNG serum concentration associated with LNG-IUS 13.5 mg (2.41 ng/L, 7 days after placement) (Supplemental Table 2). Levonorgestrel serum concentrations of 435 ± 172 ng/L at 1 month and 280 ± 123 ng/L at 3 years have been reported after placement of an LNG-containing implantable contraceptive device (Jadelle, Bayer Healthcare Pharmaceuticals Inc., Turku, Finland) (5), which are more than 3.3 times and 4.8 times higher, respectively, compared with estimated total LNG serum concentrations for LNG-IUS 13.5 mg at corresponding time points (131 ng/L at 1 month; 58.6 ng/L at 3 years) (Supplemental Table 2).

Levonorgestrel binds with high affinity to SHBG, and less than 2% of LNG is available as unbound drug in the circulation (Supplemental Table 2). Accordingly, high concentrations of SHBG in serum lead to high concentrations of total LNG concentration in serum, and vice versa (17). Changes in SHBG during treatment with an IUS can be expected to lead to changes in total LNG concentration over time, indicating nonlinear PK of LNG with respect to time; however, the effect was small (SHBG decline of approximately 15%). Therefore, only small changes in the PK of LNG are expected to occur over time during LNG-IUS use, which are not expected to be of any clinical relevance.

Individual estradiol values observed for women in these pooled analyses fell within the typical range of normal menstrual cycles. This is important because the maintenance of adequate circulating estradiol levels is an important prerequisite for a long-acting contraceptive method, to preserve normal bone health (18). The absence of a reduction in estradiol levels with the use of LNG-IUS 13.5 mg and LNG-IUS 19.5 mg are in line with data from the phase III study, which showed that LNG-IUS 13.5 mg and LNG-IUS 19.5 mg had no effect on bone mineral density (10).

Ovulation rates observed in these pooled analyses suggest that the LNG doses of all three devices do not generally reach high enough systemic levels to suppress the hypothalamicpituitary–ovarian axis. The results for LNG-IUS 20 µg/24 h are in line with previous data for this device (2, 19). Although the number of subjects was relatively low, progesterone levels indicative of anovulation were few and were mostly observed in years 1 and 2 after placement of LNG-IUS 13.5 mg and LNG-IUS 19.5 mg. This was as expected, because the release rates of LNG from LNG-IUS 13.5 mg and LNG-IUS 19.5 mg are highest initially and decline over time.

The very similar low cervical scores observed with all three LNG-IUSs indicate progestogenic effects on the cervix and cervical mucus, thereby preventing passage of the sperm through the cervical canal (20). Overall, findings were consistent with previous studies on the effects of LNG-releasing IUSs on cervical mucus (19–21).

The marked progestogenic effect on the endometrium observed with all three LNG-IUSs indicates a high degree of endometrial suppression during treatment. At baseline, a strong estrogen effect and proliferation of the endometrium was in line with the time point of collecting the endometrial histology samples within 7 days of the onset of menstrual bleeding. The strong progestin effect observed in the majority of cases during treatment is consistent with the body of literature on the mechanism of action of LNG-IUSs detailing similar morphologic changes in the endometrium, progesterone receptor binding by LNG, down-regulation of endometrial

estrogen and progesterone receptors, and an antiproliferative effect (22, 23), as well as stromal decidualization and a weak foreign body reaction (24). As reported in the phase II and phase III studies, the decrease in number of bleeding and spotting days observed reflects the high degree of endometrial suppression with all LNG IUSs evaluated (9, 10).

The main limitations of the study are the relatively low number of subjects evaluated in the detailed PK and PD analyses, which makes interpretation of the results difficult, and the fact that this was an analysis of subgroups from the phase II and III studies. Furthermore, a direct determination of the concentration of LNG in the endometrium was not possible. Release rates, which were estimated according to ex vivo LNG-IUS samples from women who prematurely discontinued the study, were used as a surrogate parameter to describe the exposure of LNG to the endometrium. A comparison with other LNG application forms is therefore not possible.

In conclusion, results from these pooled analyses of phase II and III data show that compared with LNG-IUS 20 μg/24 h, LNG-IUS 13.5 mg and LNG-IUS 19.5 mg result in a lower systemic exposure to LNG, a lower incidence of anovulation, and a similar progestin impact on the endometrium and cervical function.

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SUPPLEMENTAL TABLE 1

Definition of the Insler scoring system (14).

Parameter	0	1	2	3
Amount of mucus	NONE	SCANT A small amount of mucus can be drawn from the cervical canal	DRIBBLE A glistening drop of mucus seen in the external os; mucus easily drawn	CASCADE Abundant mucus pouring out of the external os
Spinnbarkeit	NONE	SLIGHT Uninterrupted mucus thread may be drawn approximately ¼ of the distance between the external os and vulva	MODERATE Uninterrupted mucus thread may be drawn approximately ½ of the distance between the external os and vulva	PRONOUNCED Uninterrupted mucus thread may be drawn for the whole distance between the external os and vulva
Ferning	NONE Amorphous mucus	LINEAR Fine linear ferning seen in a few spots; no side branching	PARTIAL Good ferning with side branches in parts of the slide; linear ferning or amorphous mucus in other parts	COMPLETE Full ferning of the whole preparation
Cervix	CLOSED Mucosa pale pink; the external os hardly admits a thin applicator		PARTIALLY OPEN Mucosa pink; the cervical canal easily penetrable by an applicator	GAPING Mucosa hyperemic; the external os patulous

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SUPPLEMENTAL TABLE 2

Estimated total and unbound LNG concentration at different time points after placement of LNG-IUS 13.5 mg and LNG-IUS 19.5 mg using a population PK compartmental model using samples from all subjects in the phase III study only.

Parameter	1 d	7 d	30 d	3 mo	1 y	2 y	3 y
LNG-IUS 13.5 mg							
Geometric mean total LNG (ng/L)	116	162	131	99.8	71.0	64.3	58.6
Geometric CV total LNG (%)	18.1	27.5	26.8	27.2	27.3	27.6	29.4
Geometric mean unbound LNG (ng/L)	1.67	2.41	1.98	1.49	1.05	0.947	0.871
Geometric CV unbound LNG (%)	11.1	21.4	21.6	21.5	21.3	21.4	23.1
LNG-IUS 19.5 mg							
Geometric mean total LNG (ng/L)	140	199	171	142	109	100	96.8
Geometric CV total LNG (%)	19.0	28.5	27.5	27.8	28.3	28.1	27.7
Geometric mean unbound LNG (ng/L)	2.03	2.99	2.64	2.17	1.64	1.50	1.45
Geometric CV unbound LNG (%)	12.1	22.8	23.0	22.9	22.8	22.8	22.6

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SUPPLEMENTAL TABLE 3

Mean average serum estradiol concentrations by treatment and year in phase II and III studies.

		LNG-IUS 13.5 mg		LNG-IUS 19.5 mg		LNG-IUS 20 μg/24 h	
Study	**Year**	**n**	**Mean C_{av} (SD)**	**n**	**Mean C_{av} (SD)**	**n**	**Mean C_{av} (SD)**
Phase II study	1	21	98.8 (30.8)	15	99.0 (33.2)	17	109.2 (52.3)
	2	16	112.1 (39.0)	11	93.3 (28.1)	13	130.9 (58.2)
	3	15	126.6 (53.2)	9	101.5 (27.6)	11	141.6 (83.8)
Phase III study	1	14	107.8 (42.7)	12	103.2 (23.5)		
	2	11	103.5 (19.0)	10	93.8 (20.0)		N/A
	3	11	121.6 (47.5)	7	111.7 (42.4)		

Note: N/A = not applicable.

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SUPPLEMENTAL TABLE 4

Classification of endometrium by treatment and year: pooled analysis from phase II and III studies.[a]

Time point	Parameter	LNG-IUS 13.5 mg	LNG-IUS 19.5 mg	LNG-IUS 20 μg/24 h	Total
Baseline	No. of subjects	60[b]	55[c]	32[c]	147
	Proliferative, n (%)	54 (90)	49 (89.1)	25 (78.1)	128 (87.1)
	Secretory, n (%)	5 (8.3)	5 (9.1)	5 (15.6)	15 (10.2)
Year 1	No. of subjects	54	50	31	135
	Proliferative, n (%)	0	0	0	0
	Secretory, n (%)	54 (100)	50 (100)	30 (96.8)	134 (99.3)
Year 2	No. of subjects	45	41	25	111
	Proliferative, n (%)	0	0	0	0
	Secretory, n (%)	45 (100)	41 (100)	25 (100)	111 (100.0)
Year 3	No. of subjects	49	43	23	115
	Proliferative, n (%)	0	1 (2.3)	0	1 (0.9)
	Secretory, n (%)	49 (100)	42 (97.7)	23 (100)	114 (99.1)

[a] In subjects in whom classification of endometrium was possible.
[b] One subject with atrophic endometrium at baseline.
[c] Three subjects in total with menstrual type endometrium at baseline.

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