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Levonorgestrel release rates over 5 years with the Liletta® 52-mg intrauterine system[☆,☆☆,★]

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Abstract

Objective: To understand the potential duration of action for Liletta®, we conducted this study to estimate levonorgestrel (LNG) release rates over approximately 5½ years of product use.

Methods: Clinical sites in the U.S. Phase 3 study of Liletta collected the LNG intrauterine systems (IUSs) from women who discontinued the study. We randomly selected samples within 90-day intervals after discontinuation of IUS use through 900 days (approximately 2.5 years) and 180-day intervals for the remaining duration through 5.4 years (1980 days) to evaluate residual LNG content. We also performed an initial LNG content analysis using 10 randomly selected samples from a single lot. We calculated the average ex vivo release rate using the residual LNG content over the duration of the analysis.

Results: We analyzed 64 samples within 90-day intervals (range 6–10 samples per interval) through 900 days and 36 samples within 180-day intervals (6 samples per interval) for the remaining duration. The initial content analysis averaged 52.0±1.8 mg. We calculated an average initial release rate of 19.5 mcg/day that decreased to 17.0, 14.8, 12.9, 11.3 and 9.8 mcg/day after 1, 2, 3, 4 and 5 years, respectively. The 5-year average release rate is 14.7 mcg/day.

Conclusion: The estimated initial LNG release rate and gradual decay of the estimated release rate are consistent with the target design and function of the product. The calculated LNG content and release rate curves support the continued evaluation of Liletta as a contraceptive for 5 or more years of use.

Implications statement: Liletta LNG content and release rates are comparable to published data for another LNG 52-mg IUS. The release rate at 5 years is more than double the published release rate at 3 years with an LNG 13.5-mg IUS, suggesting continued efficacy of Liletta beyond 5 years. © 2016 Elsevier Inc. All rights reserved.

Keywords: Contraception; Intrauterine device; Levonorgestrel; Liletta; Release rate

1. Introduction

Currently available hormonal intrauterine systems (IUSs) contain levonorgestrel (LNG). The amount of hormone determines the efficacy and duration of action.

Products with 13.5–52 mg of LNG are highly effective for contraception [1–3]. The local release of LNG in the uterine environment has direct effects on the cervix for pregnancy prevention and the uterus for decreasing menstrual flow [4,5]. The release rate is determined by the amount of

hormone and the characteristics of the hormone-containing membrane system.

Liletta® (known as Levosert™ in Europe) is a new 52-mg LNG-releasing IUS that has been approved for contraception for 3 years in the U.S. and several European countries with additional indications for the treatment of heavy menstrual bleeding in Europe. The initial results of the ongoing ACCESS IUS (A Comprehensive Contraceptive Efficacy and Safety Study of an IUS), used for the 3-year contraceptive indication for Liletta, have been recently reported [3]. This multicenter, Phase 3, open-label clinical trial enrolled 1751 women to receive Liletta and is designed to continue for up to 7 years of product use [3,6].

To fully understand the potential for Liletta to have a longer duration of action, we conducted this study to determine LNG content and estimate LNG release rates over approximately 5½ years of product use.

2. Materials and methods

This analysis represents a planned secondary analysis of data from the ACCESS IUS multicenter, Phase 3, open-label clinical trial of Liletta® (Medicines360, San Francisco, CA and Allergan, Irvine, CA; Liletta® is a registered trademark of Odyssea Pharma SPRL [Belgium], an Allergan affiliate). The methods of this study have been reported previously [3]. Briefly, investigators at 29 clinical sites in the United States invited healthy, nonpregnant, sexually active, nulliparous and parous women aged 16–45 years (inclusive) with regular menstrual cycles and who desired a hormonal IUS for contraception to participate. A central or local institutional review board for each center approved the study. All women signed written informed consent before study participation.

Liletta has a Nova-T polyethylene frame measuring 32 mm by 32 mm. A reservoir over the vertical stem is covered by a release rate-controlling membrane and contains LNG 52 mg. The enveloped reservoir design of the system is such that the release rate decay is expected to continue almost indefinitely without any rapid relative rate changes.

For evaluation of LNG content, clinical sites collected all study products from women who discontinued study treatment. Each collected IUS was individually sealed in a biohazard bag and labeled with the date of removal, site and subject number. Based on prior in vitro studies demonstrating stability of LNG content in Liletta through freeze and thaw cycles at −20°C, the biohazard bags were stored at approximately −20°C. Staff at each clinical site shipped specimens on dry ice at regular intervals to a drug maintenance facility for storage prior to ex vivo analysis.

We excluded IUS products from women who discontinued the study due to pregnancy. The sponsor randomly selected samples within 90-day intervals through 900 days (approximately 2.5 years) and 180-day intervals for the remaining duration through 5.4 years (1980 days). Although this sampling included the potential for different lots of product to be included, all products met the same lot release specifications and had similar content and in vitro release results. The sponsor also performed an initial LNG content analysis using 10 randomly selected samples from a single lot.

We used the measured LNG content of all samples using liquid chromatography to estimate the average in vivo drug release rate for the duration of use of the products. We plotted the drug content of each sample analyzed against the duration of exposure with an exponential best-fit regression to calculate the average rate of change of system content over time based on a monoexponential decay content model. This model is commonly used for similar types of chemical reactions that depend on the concentration of one component. Reactions whose rate depends only on the concentration of one component (first-order reactions) follow an exponential decay. The utilized model assumes that all components in the system other than LNG are static and that the rate of change is, therefore, LNG concentration driven. The average system content at time (C_t) is estimated as:

$$C_t = C_{time=0}\, e^{-kt}$$

in which k represents the best-fit exponential constant of the residual system content vs. time data. The intercept of the regression (content at time = 0) is set at the average of the initial LNG content analysis. We considered the collected sample distribution to fit the model if the majority of the samples fell within one standard deviation of predicted value based on the initial distribution (68.3% based on a normal distribution). We estimated a coefficient of determination (R^2, range 0–1) to determine the extent to which the dependent variable (residual LNG content) is predictable from the exponential regression model. We then used the estimated change in content over time to determine the average LNG release rate which can be expressed as a simple derivative:

$$Release\ rate\ (t) = \frac{d}{dt}\ (content).$$

We evaluated the statistical power of the sampling plan to estimate the release rate using simulated data with varying sizes of 6, 8 and 10 samples and intervals of 90 and 180 days, respectively. Using replicate simulation of 200 trials each, we estimated a sample plan with 6 or more samples at either interval to have more than 90% power to precisely estimate the release rate. We used SAS (Version 9.3, Cary, NC) to perform the simulations.

3. Results

We analyzed 100 samples including 64 samples within 90-day intervals (range 6–10 samples per interval) through 900 days and 36 samples within 180-day intervals (6 samples per interval) for the remaining duration. The 100 samples analyzed included 93 manufactured in a single lot in 2009 lot

and 7 from a single lot manufactured in 2012. The initial content analysis included 10 IUS products from the same lot as the 93 samples manufactured in 2009, averaging 52.0±1.8 mg (range 49.5–55.6 mg).

The best-fit curve resulted in an exponential constant $(k)=3.75\times10^{-4}$ per day (Fig. 1). Inserting this constant into the formula for average IUS content calculated LNG amounts at 1, 2, 3, 4 and 5 years of 45.3, 39.6, 34.5, 30.1 and 26.3 mg, respectively (Fig. 1). Eighty (80%) samples fit the exponential decay curve within one standard deviation, indicating the sample distribution was consistent with the model equation over time. The coefficient of determination (R^2) of 0.97 also indicated that the data are well fit by the exponential regression. We determined the average release rate by inserting the calculated exponential constant into the release rate formula:

$$Release\ rate\ (t) = -\frac{19.5\,mcg}{day}e{-3.75\times10^{-4}t}.$$

The average release rate at time 0 is calculated at 19.5 mcg/day and decreases to 17.0, 14.8, 12.9, 11.3 and 9.8 mcg/day after 1, 2, 3, 4 and 5 years, respectively (Fig. 2). The 5-year average release rate between time 0 and 5 years is 14.7 mcg/day.

4. Discussion

We found that Liletta contains approximately the same amount of LNG as another marketed LNG 52-mg IUS (52.0 mg and 51.6 mg, respectively) and the products have nearly identical initial release rates (19.5 and 19.8 mcg/day, respectively) [7]. The Liletta release rates in our analysis at 1 year and 5 years (17.0 and 9.8 mcg/day, respectively) are also similar to the rates reported for another marketed LNG 52-mg IUS (approximately 18 and 10 mcg/day, respectively) as are the average release rates over 5 years (14.7 and 14 mcg/day, respectively) [8].

The Liletta LNG release rate at 5 years is approximately the same as the reported rate estimated after 60 days of use of an LNG 13.5-mg IUS [9]. No minimum release rate for LNG IUS products has been established that correlates with a minimal efficacy rate to be included as a "highly effective" Tier 1 contraceptive by the World Health Organization and the U.S. Centers for Disease Control and Prevention [10,11]. Currently, LNG release rates as low as 5 mcg/day, which is the rate at the end of 3 years of use of the LNG 13.5-mg IUS [9], have demonstrated sufficient contraceptive efficacy to be considered Tier 1. Accordingly, the formulas derived in our analysis would suggest continued efficacy of Liletta beyond 5 years. The ACCESS IUS trial is currently continuing to follow participants for up to 7 years to provide the clinical data to support this hypothesis [3,6].

The average LNG content decreased from 52.0 to 26.3 mg (49.4%) over 5 years of study, which is proportionally equivalent to the estimated decrease in release rate from 19.5 to 9.8 mcg/day (49.7%). This observation is in accordance with Fick's first law stating that the diffusion (or in this case release) rate is proportional to the concentration gradient and therefore that the decreasing system content
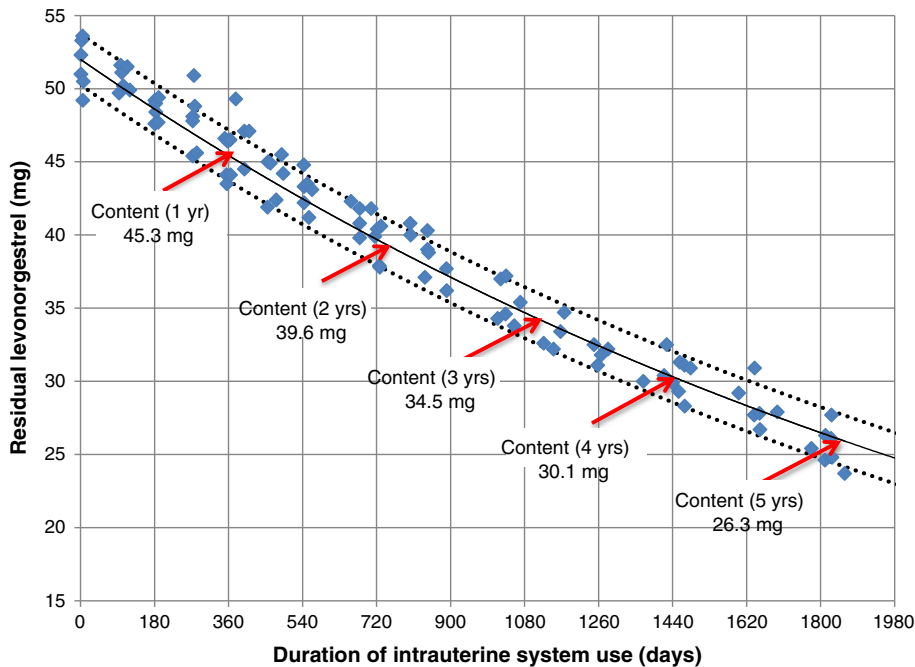

Fig. 1. LNG content of Liletta® IUSs removed or expelled over 5.4 years use. The solid line represents the mean LNG content and the dotted lines represent the standard deviation of the initial distribution calculated with the formula: Content (mg)=52.0 e$^{-3.75\ E-04\ t(day)}$. The blue diamonds are the measured LNG content measured from LNG IUSs removed or expelled over 5.4 years use.
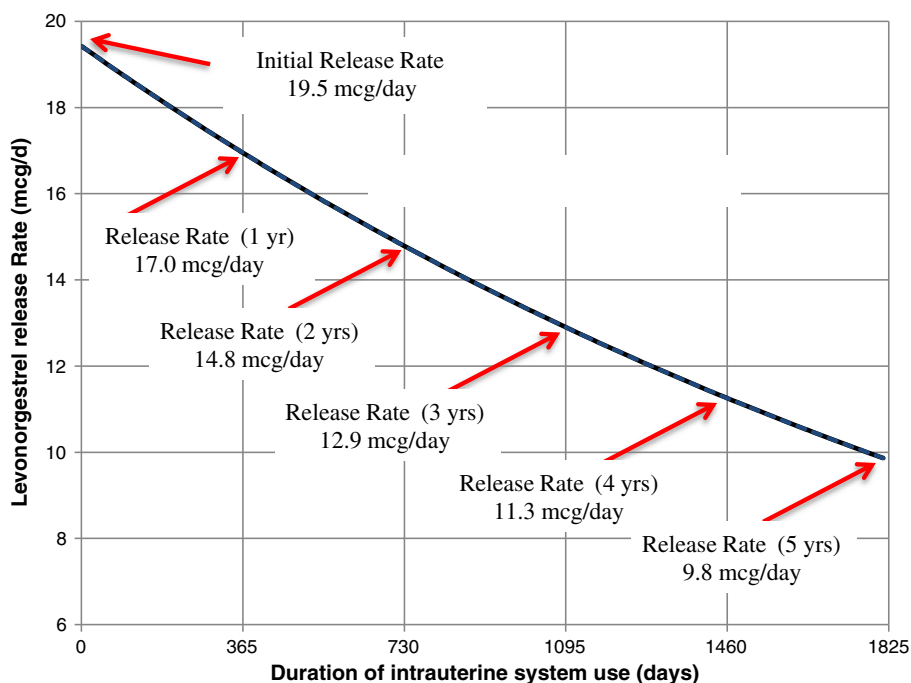
Fig. 2. LNG release rate from the Liletta® IUS over 5 years use. The solid line represents the release rate over time (*t*) calculated with the formula: Release rate (mcg/day)=19.5 e$^{-3.75 \text{ E-04 } t(day)}$.

(and therefore concentration) will result in a proportional decrease in release rate [12].

The estimated initial LNG release rate of the Liletta IUS and gradual decay of the estimated release rate are consistent with the target design and function of the product. The calculated LNG content and release rate curves support the continued evaluation of Liletta as a contraceptive beyond 5 years of use.

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