U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA Serial Number:	206229 / N000
Drug Name:	LILETTA® (Levonorgestrel-releasing intrauterine system (IUS))
Indication(s):	Prevention of Pregnancy
Applicant:	Medicines360
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1 EXECUTIVE SUMMARY

The Applicant, Medicines360, is seeking approval of LILETTA, a levonorgestrel-releasing IUS for prevention of pregnancy for up to 3 years in nulliparous and parous females of any body weight. To support this claim, the safety and efficacy data from one phase 3, open-label study M360-L102 was submitted. This review is to determine from a statistical perspective whether the submitted information supports this claim.

Study M360-L102 was a Phase 3, multi-center, open-label study to evaluate the efficacy of LILETTA, a levonorgestrel-releasing intrauterine system (LNG20 IUS), conducted in the U.S. with no restriction by weight/BMI, race or parity. Two different inserters were used to place LNG20 IUS. The original two-handed inserter (THI-001) was used for the first 760 women (b) (4) The planned study duration is at least five years, with additional follow-up of 30 days after IUS removal. The original clinical report submitted by the Applicant was using the cutoff date of 12 July 2013. However, during the 120 day safety review, additional 4 pregnancies were found in study Year 2. The agency decided to include these additional data in the final pregnancy rate calculation. Therefore the efficacy calculation for this NDA is based on the cutoff date of December 19, 2014.

There were no statistical issues in this submission. In study M360-L102, the pregnancy rates were estimated by the Pearl Index (PI) with its 95% Confidence Interval (CI) and Life Table approach. The PI and its 95% CI in the LNG20 MITT population are 0.15 (95% CI: 0.02, 0.55), 0.41 (95% CI: 0.11, 1.05), and 0.00 (95% CI: 0.00, 0.98) at Year 1, Year 2 and Year 3, respectively. The cumulative pregnancy rate in the three year study using Life Table approach in the LNG20 MITT population is 0.55 (95% CI: 0.24 to 1.23). The point estimates estimated by both Pearl Index and life table method were ≤ 0.55 with the upper bound of the 95% CI that did not exceed 1.23, a threshold generally considered acceptable for IUS contraceptives.

From a statistical perspective, the Applicant reported efficacy results based on pre-specified endpoint and statistical methods. Both the Pearl Index and life table method consistently showed that LNG20 IUS was effective in preventing pregnancy for up to three years of product use.

2 INTRODUCTION

2.1 Overview

The Applicant, Medicines360, is seeking approval of LILETTA, a Levonorgestrel-releasing intrauterine system. Levonorgestrel is a progestin which has been used in a number of FDA approved hormonal contraceptives. LILETTA is indicated as an intrauterine contraceptive to last for a period of 3 years in both nulliparous and parous females of any body weight.

The efficacy and safety of LILETTA was assessed in one phase 3 study. Study M360-L102 was an open-label, multicenter study to evaluate the efficacy of a levonorgestrel-releasing intrauterine system (LNG20) in nullparous and parous females of child-bearing potential who request long-term, reversible contraception. The planned study duration is at least five years, with additional follow-up of 30 days after IUS removal. The original submitted report provides efficacy results for the first 36 months of study participation through the cutoff date of 12 July 2013. Table 1 presents a brief summary of the study.

Table 1: Brief summary of the phase 3 Study M360-L102

Study Number (No. of Sites / Country) Dates of Study Conduct	Subject Population	Treatments	Enrolled (ITT)	Duration of Treatment	Design[1]
M360-L102 (29 / U.S.) 12-28-09 to 07-12-13	Nulliparous and parous females of child-bearing potential who request long-term, reversible contraception with 16-45 years of age	LNG20 IUS	1,751 (1,691)	up to three years of LNG20 IUS	OL, MC, U

[1] OL = Open Label, MC = Multicenter, U = Uncontrolled,

2.2 Data Sources

The study reports and the data sets were submitted electronically to the Electronic Document Room. The SAS data sets were complete and well documented.

The study reports for study M360-L102 are located at:
\\CDSESUB1\evsprod\NDA206229\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\contraception\5351-stud-rep-contr\eff-safety\l102

The datasets and programs for study M360-L102 are located at:
\\CDSESUB1\evsprod\NDA206229\0000\m5\datasets\l102
And
\\CDSESUB1\evsprod\NDA206229\0004\m5\datasets\l102\analysis\adam\programs

3 STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Study Design and Endpoints

Study M360-L102 was an open-label, multicenter study to evaluate the efficacy of LILETTA, a levonorgestrel-releasing intrauterine system (LNG20 IUS), in both nullparous and parous females of child-bearing potential who request long-term, reversible contraception. The study was conducted at 29 clinical sites in the United States.

Study M360-L102 enrolled 1,910 subjects into the study. This included 1,751 women ages 16 to 45 assigned to the LNG20 IUS, among which 58% (1,011) were nulliparous and 42% (740) were parous women. Two different inserters were used to place LNG20 IUS. The original two-handed inserter (THI-001) was used for the first 760 women (b) (4)

Subjects were to be evaluated during study treatment use for up to 60 months. However, this report is based on the first 36 months of subject participation for efficacy. Results for subsequent years of product use will be provided in follow-up reports. Study efficacy assessments included in this report were performed at a clinic visit at Screening/Enrollment and Months 1, 3, 6, 12, 18, 24, 30, and 36, with subsequent assessments performed at Months 42, 48, 54 and 60 to be presented in follow-up reports. Telephone assessments occurred at 3-month intervals between scheduled study visits, starting at Month 9. All pregnancies that occurred during treatment (with date of conception while the IUS was in the subject and up to and including 7 days after IUS discontinuation) were to be followed to completion and the outcome recorded.

The primary objectives of study M360-L102 was to assess the efficacy of LILETTA (LNG20 IUS), a levonorgestrel (LNG)-releasing intrauterine system (IUS), in nullparous and parous females of child-bearing potential who request long-term, reversible contraception.

The following subject populations were used for efficacy analyses:

- The Modified Intent-to-Treat (MITT) population included all subjects between 16-35 years of age at study entry for whom the assigned IUS was successfully placed in the uterus and for whom there was at least one assessment of pregnancy status after placing the IUS.
- The Per-Protocol (PP) population included subjects in the MITT population with no major protocol deviations

3.1.2 Statistical Methodologies

The primary efficacy variable is the pregnancy rate calculated by the Pearl Index (PI), an estimation of the number of unintended pregnancies per 100 women-years of exposure. The Pearl Index is calculated as the number of "on treatment" pregnancies in the study divided by the total number of complete 28-day cycles of use in the study across all participating subjects, that result multiplied by 1300 (13 cycles x 100 years). Complete cycles were counted as consecutive 28-day intervals based on the number of days duration between IUS placement and the date of IUS discontinuation. In the

case of subjects who were still on study at the time of a Pearl Index calculation, the last study visit date when a pregnancy test was performed was used in place of the IUS discontinuation date. A "last cycle" computed using this algorithm was considered complete if it was at least 23 days in length. In addition, subjects who became pregnant had that last cycle counted as completed for the PI calculation, regardless of length.

For the primary PI outcome using exposure information for Year 1, Year 2 and Year 3, the Modified Intent-to-Treat (MITT) population was used as the basis of exposure and all 28-day cycles (except the first 28-day cycle) where use of another birth control method was reported in the daily diary were excluded from the total cycle count denominator.

For the definitive assessment of contraceptive efficacy, the Pearl Index and its 95% confidence interval were considered the primary result for inferences.

The "on-treatment" pregnancy rate and its associated 95% confidence interval were also estimated using life table methods with year of use serving as the principal life-table classification. Because the life-table method depends on a continuous exposure interval, it did not exclude 28-day cycles in which another birth control method was reported, i.e., all complete 28-day cycles were used in the calculations.

Life Table analysis was conducted on the following populations:

- LNG20 MITT with no cycle exclusions for Year 1, Year 2 and Year 3
- LNG20 MITT subgroups (age, parity, race, BMI, inserter type)
- LNG20 IUS subjects 36-45 years old with no cycle exclusions

Life table-derived rates are also provided for the MITT population by:

- Age (completed years):< 18, 18-30, 31-35
- Parity: nulliparous versus parous
- Race: White versus Non-white
- Body Mass Index: ≤ 24.9, 25.0−29.9, 30.0−39.9, ≥ 40

3.1.3 Patient Disposition, Demographic and Baseline Characteristics

A total of 2,074 subjects were screened for the study. 1,910 generally health subjects aged 16-45 were enrolled into the study, 1,751 of whom had at least one placement attempt with LNG20 IUS. Table 2 summarizes the number of subjects and the disposition of LNG20 IUS treated subjects 16-35 years of age. The primary reason for study discontinuation in study M360-L102 after a successful placement of IUS are "Adverse Event" (9.2%) and loss to follow-up (5%). The number of subjects who finished at least 1 year, 2 year and 3 year study duration (MITT population) are 694, 383, and 272, respectively.

Table 2: Subject Disposition: Study M360-L102

Screened Population	2,074
Enrolled/Safety Population	1,751
Discontinued After Failed IUD Placement	37
ITT – IUD Placed with 1+ Pregnancy Assessment	1,691 (96.6)
MITT – ITT Ages 16-35	1,545 (96.6)
Complete 1+ Year Study	694 (43.4%)
Complete 2+ Year Study	383 (23.9%)
Complete 3+ Year Study	272 (17.0%)
IUS Expulsion/Removal	427
Reason for IUS Discontinued*	
Desires Pregnancy	60 (3.8)
Expulsion of IUS	45 (2.9)
Adverse Event	145 (9.2)
Investigator Decision	10 (0.6)
IUS No Longer 1st Method of Contraception	7 (0.4)
Sponsor Decision	2 (0.1)
Subject Relocation	29 (1.8)
Subject Withdrew Consent	18 (1.1)
Lost to Follow-Up	79 (5.0)
Other	32 (2.0)

* Only applicable for subjects who have a successful placement and discontinued. Percentage based on the total number of treated subjects within each corresponding treatment group.
(Source: Clinical Study M360-L102 Report; Table 4, page 87 & Reviewer's Analysis)

Demographic and gynecological histories of MITT population are presented in Table 3. The mean age was 26.2 years (range 16 – 35). The majority of patients were white (78.6%) and African American (12.9%). The mean BMI of the patients was 26.8 (range 15.8 – 60.4). There were 29.3% women with BMI greater than 30 kg/m^2.The average menstrual cycle length reported at inclusion was 28.4 days with an average of 4.4 bleeding days. The primary contraceptive method was condom alone (32.2%) and combination oral contraceptive (30.2%) in the 3 months preceding enrollment. The study population was representative of US demographics.

Table 3: Demographics and Baseline Characteristics (MITT): Study M360-L102

Variables	MITT Population (N=1,545)
Age (Years)	Mean (±SD) 26.2±4.4 Median Age=26 Min-Max=16-35
Age Category	
16-18	11 (0.6%)
18 and older	1,534
Race	
White	1,211 (78.6%)
African American	199 (12.9%)
Asian	60 (3.9%)
Other	75 (4.9%)
Body Mass index (kg/m^2)	Mean (±SD) 26.8±6.7 Median BMI=24.8 Min-Max=15.8-60.4
BMI 25-29.9	373 (24.2%)
BMI ≥ 30	374 (24.3%)
BMI ≥40	77 (5.0%)
Nulliparous	954 (61.7%)
Average menstrual length (days)	Mean (±SD) 28.4±2.9
Average duration of menstrual flow (days)	Mean (±SD) 4.4±2.1
Previous pregnancy	49.4%
Previous Contraceptive	
Combination Oral Contraceptive	466 (30.2%)
Condom Alone	498 (32.2%)

(Source: Adapted from Clinical Study M360-L102 Report; Table 8, Table 10, Table 11 & Table 13)

3.1.4 Results and Conclusions

Data from the 16 to 45 years of age LNG20 treated ITT population are analyzed for efficacy. The primary efficacy is based on Pearl Index and Life table approach in the MITT population of women 35 years of age or less. No PP population analysis is conducted because there are only 3 subjects (< 0.2%) in the MITT population with major protocol deviations that could impact the efficacy outcome.

The original clinical report submitted by the Applicant was using the cutoff date of 12 July 2013. However, during the 120 day safety review, additional 4 pregnancies were found in study Year 2. The agency decided to include these additional data in the final pregnancy rate calculation. Therefore the efficacy calculation for this NDA is based on the cutoff date of December 19, 2014.

Table 4 presents the Pearl Index results for LNG20 in ITT and MITT population in the three year study. There were only 2 on-treatment pregnancies in the first year and 4 additional on-treatment pregnancies in the second year in the LNG20 IUS treated ITT and MITT population. The PI and 95% confidence intervals (CI) in the LNG20 MITT population of 1,545 eligible subjects are 0.15 (95% CI: 0.02, 0.55), 0.41 (95% CI: 0.11, 1.05), and 0.00 (95% CI: 0.00, 0.98) at Year 1, Year 2 and Year 3, respectively. The cumulative PI from Year 1 to Year 3 is 0.22 (95% CI: 0.08, 0.49). These results are confirmed by this reviewer.

Table 4: Pregnancy Rates for All LNG20 Treated Subjects: Study M360-L102

	Population	N	On-Treatment Pregnancies	Number of Cycles	Pearl Index	95% Confidence Interval
Year 1	ITT - All Subjects	1,691	2	18,820	0.14	(0.02, 0.50)
	MITT - ITT ages 16-35	1,545	2	17,125	0.15	(0.02, 0.55)
Year 2	ITT - All Subjects	1,318	4	14,217	0.37	(0.10, 0.94)
	MITT - ITT ages 16-35	1,195	4	12,694	0.41	(0.11, 1.05)
Year 3	ITT - All Subjects	591	0	6,088	0.00	(0.00, 0.80)
	MITT - ITT ages 16-35	496	0	4,892	0.00	(0.00, 0.98)
Year 1 to Year 3	ITT - All Subjects	1,691	6	39,018	0.20	(0.07, 0.44)
	MITT - ITT ages 16-35	1,545	6	34,711	0.22	(0.08, 0.49)

(Source: Reviewer's and Sponsor's Analyses)

As presented in Table 5, the cumulative pregnancy rates in MITT population using Life table approach are 0.14 (95% CI: 0.04 to 0.57), 0.55 (95% CI: 0.24 to 1.23), and 0.55 (95% CI: 0.24 to 1.23) for Year 1, Year 2 and Year 3, respectively.

Table 5: Life Table Analysis: Study M360-L102

	Population	N	Cumulative Pregnancy Rate	95% Confidence Interval
Year 1	ITT - All Subjects	1,691	0.13	(0.03, 0.52)
	MITT - ITT ages 16-35	1,545	0.14	(0.04, 0.57)
Year 2	ITT - All Subjects	1,691	0.49	(0.22, 1.10)
	MITT - ITT ages 16-35	1,545	0.55	(0.24, 1.23)
Year 3	ITT - All Subjects	1,691	0.49	(0.22, 1.10)
	MITT - ITT ages 16-35	1,545	0.55	(0.24, 1.23)

(Source: Reviewer's and Sponsor's Analyses)

The PI point estimates and cumulative pregnancy rates using life table method were ≤ 0.55 and the upper bound of the 95% CI has not exceeded 1.23, a threshold generally considered acceptable for IUS contraceptives. Both analyses consistently demonstrated that LNG20 IUS was effective in preventing pregnancy for up to three years of product use.

3.2 Evaluation of Safety

Safety information can be found in the clinical reviewer's report.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, Geographic Region and others

The efficacy results were based on women aged 16 to 35 only so the subgroup analyses by gender and age were not necessary for this indication. The phase 3 study was conducted in the US so no by-region analysis was necessary.

There were only 2 on-treatment pregnancies in Year 1 and 4 additional on-treatment pregnancies in Year 2 in the LNG20 IUS treated ITT and MITT population, they were all white female and only one pregnancy with BMI greater than 30kg/m^2. Due to the very low pregnancy rate, subgroup analyses by race, BMI and others are not necessary. LNG20 IUS is efficacious in all subgroups.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

There were no statistical issues in this submission. Efficacy was evaluated by the pregnancy rate based on the Pearl Index and Life Table approach in women aged 16 to 35 years excluding cycles (except the first 28-day cycle) with no intercourse and where other birth control methods were used and life table analysis. In study M360-L102, the PI and its 95% CI in the LNG20 MITT population are 0.15 (95% CI: 0.02, 0.55), 0.41 (95% CI: 0.11, 1.05), and 0.00 (95% CI: 0.00, 0.98) at Year 1, Year 2 and Year 3, respectively. The cumulative pregnancy rate in the three year study using Life Table approach in the LNG20 MITT population is 0.55 (95% CI: 0.24 to 1.23).

5.2 Conclusions and Recommendations

From a statistical perspective, the Applicant reported efficacy results based on pre-specified endpoint and statistical methods. Both the Pearl Index and life table method consistently showed that LNG20 IUS was effective in preventing pregnancy for up to three years of product use.

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/s/

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02/23/2015

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