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Food and Drug Administration
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STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA Serial Number:	206229 / S008
Drug Name:	Liletta® (levonorgestrel-releasing intrauterine system, 52 mg)
Indication(s):	Prevention of Pregnancy for up to 6 Years
Applicant:	Medicines360
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1 EXECUTIVE SUMMARY

The Applicant, Medicines360, is seeking the extended use of Liletta, a levonorgestrel-releasing intrauterine system (IUS), for prevention of pregnancy for up to six years. Liletta was approved for prevention of pregnancy for up to five years on October 15, 2018. To support the current extension, up to six years safety and efficacy data through August 20, 2018 from the ongoing Study M360-L102 has been submitted.

Study M360-L102 is a Phase 3, multi-center, open-label study conducted in the U.S. subjects with no restriction by weight, BMI, race, or parity. A total of 1751 subjects had at least one placement attempt with Liletta. Three hundred and twenty-one (32)1 women 16 to 35 years of age at enrollment used Liletta for six years.

There were no statistical issues with regards to efficacy evaluation for the current extension data in this submission. The efficacy was evaluated by the pregnancy rate based on the Pearl Index in subjects aged 16 to 35 years excluding cycles in which other birth control methods were used unless a pregnancy occurred in that cycle. The pregnancy rates estimated by Pearl Index and associated 95% confidence interval are 0.15 (0.02, 0.55), 0.37 (0.10, 0.94), 0.11 (0, 0.62), 0.13 (0, 0.74), 0.16 (0, 0.87), and 0 (0, 0.94) at Year 1, Year 2, Year 3, Year 4, Year 5, and Year 6, respectively. The cumulative pregnancy rate for six years using life table approach in subjects aged 16 to 35 years is 0.87 (0.44, 1.70). From a statistical perspective, efficacy assessed by both the Pearl Index and life table method consistently showed that Liletta was effective in preventing pregnancy for up to six years.

2 INTRODUCTION

2.1 Overview

Liletta, a levonorgestrel-releasing intrauterine system, was approved for prevention of pregnancy for up to five years in both nulliparous and parous women of any body weight. In this sNDA, the Applicant is seeking to extend the duration of use for up to six years. To support the current extension, up to six years of safety and efficacy data through August 20, 2018 from the ongoing Study M360-L102 has been submitted.

Study M360-L102 is a Phase 3, multi-center, open-label study conducted in the U.S. in subjects with no restriction by weight, BMI, race, or parity. A total of 1751 subjects had at least one placement attempt with Liletta (1600 subjects aged 16 to 35 years, 151 aged 36 to 45 years) and 159 had at least one placement attempt with Mirena. Among the 1600 subjects, 1545 were included in the Liletta modified intent-to-treat (MITT) population which included all subjects between 16 and 35 years of age at study entry for whom Liletta was successfully placed in the uterus and for whom there was at least one assessment of pregnancy status after placing Liletta. Two different inserters were used to place Liletta IUS: the original two-handed inserter (THI-001) was used for the first 760 subjects and a single-handed inserter (SHI-001) was used for the 991 subsequently enrolled subjects.

Table 1 presents a summary of the study data in current submission.

Table 1: Summary of the Phase 3 Study M360-L102

Study Number (No. of Sites / Country) Dates of Study Conduct	Subject Population	Treatments	Liletta Safety/ MITT	Duration of Treatment	Design[1]
M360-L102 (30 / U.S.) December 28, 2009 to August 20, 2018	Nulliparous and parous subjects of child-bearing potential who request long-term, reversible contraception with of age	Liletta	1751 (1545)	Up to 6 years	OL, MC, U

[1] OL = Open Label, MC = Multicenter, U = Uncontrolled.
Liletta Safety Population included all enrolled subjects who underwent Liletta placement procedure, regardless of age and outcome. Liletta MITT Population included all subjects between 16 and 35 years of age at study entry for whom Liletta was successfully placed in the uterus and for whom there was at least one assessment of pregnancy status after placing Liletta.

2.2 Data Sources

The study reports and the data sets were submitted electronically to the Electronic Document Room. The SAS data sets and associated documentations were clear and complete. The study reports, datasets, and SAS programs for study M360-L102 with cutoff date of August 20, 2018 are located at: \\CDSESUB1\evsprod\NDA206229\0093.

3 STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Study Design and Endpoints

Study M360-L102 is an open-label, multicenter study to evaluate the efficacy and safety of Liletta in both nulliparous and parous subjects of child-bearing potential who request long-term reversible contraception. The study was conducted at 30 clinical sites in the U. S.

Subjects were to be evaluated during study treatment use for up to 121 months. In this submission, the study report is based on the first 72 months of subject participation for efficacy and safety including all data obtained through the data cutoff date regardless of duration of exposure, and those occurring within 30 days after IUS discontinuation in subjects discontinued on or before August 20, 2018. Study efficacy assessments were performed at a clinic visit at Screening/Enrollment and Months 1, 3, 6, and every six months till Month 72 with subsequent assessments every six months till Month 121 to be presented in follow-up reports. Telephone assessments occurred at 3-month intervals between scheduled study visits, starting at Month 9. All subjects had a 30-Day Safety Follow-up Visit one month after discontinuing the study treatment for safety assessments. Unscheduled visits were permitted when subjects reported problems related to safety, the IUS, or study participation or for repeat laboratory tests.

Pregnancies that occurred during study treatment or after IUS discontinuation through the 30-Day Safety Follow-up Visit were identified through subject query and urine and serum pregnancy testing. A transvaginal ultrasound was performed for pregnancy dating and to verify if

the IUS was still present in the uterus. 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.

3.1.2 Study Endpoints and Statistical Methodologies

The primary efficacy variable is the pregnancy rate calculated by the Pearl Index, 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 between IUS placement and the date of IUS discontinuation. All the 28-day cycles where use of another birth control method was reported in the daily diary were excluded from the total cycle count denominator. The Pearl Index and associated 95% confidence interval was calculated using both the cumulative data through Year 6 and as individual, non-cumulative year-by-year estimates.

The “on-treatment” pregnancy rate and 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. The life table efficacy analyses were conducted by subgroups on age group, race, parity, and other baseline characteristics.

Liletta Safety Population included all enrolled subjects who underwent Liletta placement procedure, regardless of age and outcome. The Liletta MITT Population included all subjects between 16 and 35 years of age at study entry for whom Liletta was successfully placed in the uterus and for whom there was at least one assessment of pregnancy status after placing Liletta.

In this review, the efficacy analyses are based on the Liletta MITT population. Patient disposition, demographic, and baseline characteristics are based on Liletta Safety Population.

3.1.3 Subject Disposition, Demographic and Baseline Characteristics

Table 2 summarizes the subject disposition from the Liletta safety population. A total of 1751 subjects (1600 subjects 16-35 years old and 151 subjects 36-45 years old) had at least one placement attempt with Liletta. 1545 subjects were in the Liletta MITT population. The number of subjects who finished at least 1 year, 2 years, 3 years, 4 years, 5 years, and 6 years study duration are 1401, 1149, 965, 818, 689, and 402 respectively. The primary reasons for study discontinuation in study M360-L102 after a successful placement of IUS are “Desires Pregnancy” (15.5%), “Adverse Event” (15.2%), other reasons (11.9%), and loss to follow-up (11.8%).

Table 2: Subject Disposition (Liletta Safety Population)

	16-35 years N (%)	36-45 years N (%)	Total N (%)
Enrolled/Safety Population[1]	1600 (100%)	151 (100%)	1,751 (100%)
MITT Population	1545 (96.6%)		
Discontinued after Failed Insertion	32 (2.0%)	5 (3.3%)	37 (2.1%)
Completed Month 12	1276 (79.8%)	125 (82.8%)	1401 (80.0%)
Month 24	1035 (64.7%)	114 (75.5%)	1149 (65.6%)
Month 36	860 (53.8%)	105 (69.5%)	965 (55.1%)
Month 48	720 (45.0%)	98 (64.9%)	818 (50.3%)
Month 60	598 (37.4%)	91 (60.3%)	689 (39.3%)
Month 72	321 (20.1%)	81 (53.6%)	402 (23.0%)
IUS Expulsion/Removal	1132 (72.2%)	122 (83.6%)	1254 (73.2%)
Reason for IUS Discontinuation[2]			
Completed Full Protocol	0	45 (30.8%)	45 (2.6%)
Desires Pregnancy	261 (16.6%)	4 (2.7%)	265 (15.5%)
Pregnancy with IUS in Place	1 (0.1%)	0	1 (0.1%)
Expulsion of IUS	61 (3.9%)	7 (4.8%)	68 (4.0%)
Adverse Event[3]	238 (15.2%)	25 (15.8%)	261 (15.2%)
Investigator Decision	13 (0.8%)	2 (1.4%)	15 (0.9%)
IUS No Longer 1st Method of Contraception	20 (1.3%)	0	20 (1.2%)
Sponsor Decision	5 (0.3%)	0	5 (0.3%)
Subject Relocation	107 (6.8%)	4 (2.7%)	111 (6.5%)
Subject Withdrew Consent	52 (3.3%)	4 (2.7%)	56 (3.3%)
Lost to Follow-Up	188 (12.0%)	15 (10.3%)	203 (11.8%)
Other	186 (11.9%)	18 (12.3%)	204 (11.9%)

[1] The denominator for percentages is the number of subjects in the safety population.

[2] The denominator for percentages is the number of subjects in the safety population who had a successful insertion (N=1568).

[3] IUS expulsions were not included.

(Source: Study M360-L102 Clinical Study Report; Tables 1.1 and 1.2, and Reviewer's Analysis)

Table 3 summarizes the demographic and baseline characteristics for Liletta safety population. The median age at enrollment was 27.3 years old. 78.4% of subjects were white, 13.3% were Black or African-American. 14.7% was Hispanic or Latina. Almost one-fourth (24.4%) were defined as overweight (BMI 25-29.9 kg/m^2), one-fourth (25.1%) were defined as obese (BMI ≥ 30 kg/m^2) and 5.3% morbidly obese (BMI ≥ 40 kg/m^2). 58.3% reported living with their partner.

3.1.4 Results and Conclusions

Table 4 presents the pregnancy rated estimated by Pearl Index for the Liletta MITT population in the six-year data using cutoff date of August 20, 2018. There were two on-treatment pregnancies in the first year, four additional on-treatment pregnancies in the second year, one additional pregnancy in third, fourth, fifth year, and no pregnancy in the sixth year. The pregnancy rates based on Pearl Index and associated 95% confidence intervals excluding cycles where other birth control methods were used are 0.15 (0.02, 0.55), 0.37 (0.10, 0.94), 0.11 (0.00, 0.62), 0.13 (0.00, 0.74), and 0.16 (0.00, 0.87), 0 (0, 0.94) at Year 1, Year 2, Year 3, Year 4, Year 5, and Year 6,

respectively. The 6-year cumulative pregnancy rate by Pearl Index is 0.18 (0.08, 0.33, See Table 5).

Table 3: Demographics and Baseline Characteristics for Subjects 16-35 Years of Age (Liletta Safety Population)

	16-35 years (N=1600)	36-45 years (N=151)	Total (N=1,751)
Age (years)			
Mean (SD)	26.2 (4.4)	39.6 (2.7)	27.3 (5.7)
Median	26	39	26
Ethnicity			
Hispanic or Latina	237 (14.8%)	21 (13.9%)	258 (14.7%)
Race			
American Indian or Alaska Native	19 (1.2%)	2 (1.3%)	21 (1.2%)
Asian	61 (3.8%)	7 (4.6%)	68 (3.9%)
Black or African American	212 (13.3%)	20 (13.2%)	232 (13.3%)
Native Hawaiian or Other Pacific Islander	5 (0.3%)	1 (0.7%)	6 (0.3%)
White	1250 (78.3%)	120 (79.5%)	1370 (78.4%)
Multiple Races Indicated	49 (3.1%)	1 (0.7%)	0
BMI			
N	1596	151	1747
Mean (SD)	26.8 (6.7)	28.6 (7.6%)	26.9 (6.8%)
Median	24.8	26.3	24.9
Min, Max	15.8, 60.4	17, 61.6	15.8, 61.6
BMI 25-29.9	390 (24.4%)	37 (24.5%)	427 (24.4%)
BMI ≥ 30	383 (24.0%)	55 (36.4%)	438 (25.1%)
BMI ≥ 40	79 (4.9%)	14 (9.3%)	93 (5.3%)
Partner Status			
Lives with Partner	915 (57.2%)	106 (70.2%)	1021 (58.3%)
Does Not Live with Partner	685 (42.8%)	45 (29.8%)	730 (41.7%)
Nulliparous	989 (61.8%)	22 (14.6%)	1011 (57.7%)
Age (years) Mean (SD)	24.8 (3.8)	38.7 (3.0)	25.1 (4.3)
Median	24	38	25
Parous	611 (38.2%)	129 (85.4%)	740 (42.3%)
Age (years) Mean (SD)	28.3 (4.5)	39.8 (2.6)	30.3 (6.1)
Median	29	39	30

Note: Percentage based on the number of subjects in the safety population.
(Source: Study M360-L102 Clinical Study Report Table 8 and Reviewer's Analysis)

Table 4: Yearly Pearl Index for Liletta in Subjects 16-35 Years of Age (MITT)

	On-Treatment Pregnancies	Number of Cycles	Pearl Index (95% CI)
Year 1	2	17175	0.15 (0.02, 0.55)
Year 2	4	14205	0.37 (0.10, 0.94)
Year 3	1	11760	0.11 (0.00, 0.62)
Year 4	1	9891	0.13 (0.00, 0.73)
Year 5	1	8335	0.16 (0.00, 0.87)
Year 6	0	5091	0.00 (0.00, 0.94)

(Source: CSR Table 10.3.1 and reviewer's analysis, excluding cycles where other birth control methods were used.)

Table 5: Cumulative Pearl Index for Liletta in Subjects 16-35 Years of Age (MITT)

	On-Treatment Pregnancies	Number of Cycles	Pearl Index (95% CI)
1 Year	2	17175	0.15 (0.02, 0.55)
2 Years	6	31380	0.25 (0.09, 0.54)
3 Years	7	43140	0.21 (0.08, 0.43)
4 Years	8	53031	0.20 (0.08, 0.39)
5 Years	9	61366	0.19 (0.09, 0.36)
6 Years	9	66457	0.18 (0.08, 0.33)

(Source: CSR Table 10.1.1 and reviewer's analysis, excluding cycles where other birth control methods were used.)

As presented in Table 6, the cumulative pregnancy rates in the Liletta MITT population using life table approach with no cycles excluded are 0.14 (0.04 to 0.57), 0.49 (0.22 to 1.09), 0.59 (0.28 to 1.25), 0.72 (0.36 to 1.45), 0.87 (0.44, 1.70), and 0.87 (0.44, 1.70) for 1 year, 2 years, 3 years, 4 years, 5 years, and 6 years, respectively.

Table 6: Cumulative Pregnancy Rate for Liletta Subjects 16-35 Years of Age (MITT)

	Number of Cycles	Cumulative Pregnancy Rate (95% CI)
1 Year	18080	0.14 (0.04, 0.57)
2 Years	32559	0.49 (0.22, 1.09)
3 Years	44547	0.59 (0.28, 1.25)
4 Years	54624	0.72 (0.36, 1.45)
5 Years	63119	0.87 (0.44, 1.70)
6 Years	68288	0.87 (0.44, 1.70)

(Source: CSR Tables 11.1 and reviewer's analysis. No cycles were excluded.)

The pregnancy rates estimated by Pearl Index and cumulative pregnancy rates using life table method consistently demonstrated that Liletta was effective in preventing pregnancy for up to six years of product use.

3.2 Evaluation of Safety

Safety information is in the clinical reviewer's report.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Due to small number of pregnancies, the pregnancy rate estimation by subgroup is for presentation purpose only. The life table efficacy analyses by subgroups of age, race, parity status, BMI, and inserter types are presented in Table 7 in the Appendix. The results by the subgroup are consistent with the overall analyses.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

There were no statistical issues identified in this submission. Efficacy was evaluated by the pregnancy rate based on the Pearl Index excluding cycles where other birth control methods were used and life table method with no cycles excluded. The pregnancy rates and associated 95% confidence intervals in the Liletta MITT population of 1545 subjects are 0.15 (0.02, 0.55), 0.37 (0.10, 0.94), 0.11 (0.00, 0.62), 0.13 (0.00, 0.73), 0.16 (0.00, 0.87), and 0.00 (0.00, 0.94) at Year 1, Year 2, Year 3, Year 4, Year 5, and Year 6, respectively. The 6-year cumulative pregnancy rate by Pearl Index is 0.18 (0.08, 0.33). The 6-year cumulative pregnancy rate using life table approach is 0.87 (0.44, 1.70).

5.2 Conclusions and Recommendations

From a statistical perspective, both the Pearl Index and life table method consistently showed that Liletta was effective in preventing pregnancy for up to six years of use.

Appendix

Table 7: Cumulative Pregnancy Rate for Liletta Subjects 16-35 Years of Age by Subgroup (MITT)

		1 Year	2 Years	3 Years	4 Years	5 Years	6 Years
Age Group (Years)	**< 18 (N=11)**	0	0	0	0	0	0
	18-30 (N=1230)	0.09 (0.01, 0.64)	0.42 (0.16, 1.12)	0.55 (0.23, 1.34)	0.72 (0.32, 1.61)	0.91 (0.42, 1.95)	0.91 (0.42, 1.95)
	31-35 (N=304)	0.36 (0.05, 2.50)	0.78 (0.19, 3.09)	0.78 (0.19, 3.09)	0.78 (0.19, 3.09)	0.78 (0.19, 3.09)	0.78 (0.19, 3.09)
Race	**White (N=1255)**	0.17 (0.04, 0.69)	0.60 (0.27, 1.32)	0.72 (0.34, 1.52)	0.72 (0.34, 1.54)	0.90 (0.44, 1.84)	0.90 (0.44, 1.84)
	Non-White (N=286)	0	0	0	0.75 (0.11, 5.18)	0.75 (0.11, 5.18)	0.75 (0.11, 5.18)
Parity Status	**Nulliparous (N=954)**	0	0.27 (0.07, 1.07)	0.43 (0.14, 1.33)	0.43 (0.14, 1.33)	0.66 (0.24, 1.79)	0.66 (0.24, 1.79)
	Parous (N=591)	0.38 (0.10, 1.53)	0.88 (0.33, 2.34)	0.88 (0.33, 2.34)	1.25 (0.51, 3.06)	1.25 (0.51, 3.06)	1.25 (0.51, 3.06)
BMI (kg/m^2)	**≤24.9 (N=795)**	0.14 (0.02, 0.97)	0.63 (0.24, 1.68)	0.83 (0.35, 2.00)	1.07 (0.48, 2.41)	1.37 (0.64, 2.93)	1.37 (0.64, 2.93)
	25.0 – 29.9 (N=373)	0.30 (0.04, 2.08)	0.30 (0.04, 2.08)	0.30 (0.04, 2.08)	0.30 (0.04, 2.08)	0.30 (0.04, 2.08)	0.30 (0.04, 2.08)
	30.0 – 39.9 (N=297)	0	0	0	0	0	0
	≥ 40 (N=77)	0	1.72 (0.24, 11.62)	1.72 (0.24, 11.62)	1.72 (0.24, 11.62)	1.72 (0.24, 11.62)	1.72 (0.24, 11.62)
Inserter Type	**THI-001 (N=611)**	0.18 (0.03, 1.29)	0.18 (0.03, 1.29)	0.18 (0.03, 1.29)	0.54 (0.13, 2.30)	0.97 (0.30, 3.16)	0.97 (0.30, 3.16)
	SHI-001 (N=934)	0.12 (0.02, 0.82)	0.67 (0.28, 1.61)	0.84 (0.38, 1.86)	0.84 (0.38, 1.86)	0.84 (0.38, 1.86)	0.84 (0.38, 1.86)

(Source: Tables 11.2, 11.3, 11.4, 11.5, and 11.6 in the Clinical Study Report. No cycles were excluded.)

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