CLINICAL REVIEW

Application Type	NDA Efficacy Supplement
Application Number(s)	206229 (S008)
Priority or Standard	Standard
Submit Date(s)	December 26, 2018
Received Date(s)	December 26, 2018
PDUFA Goal Date	October 26, 2019
Division/Office	Division of Bone, Reproductive, and Urologic Products (DBRUP) Office of Drug Evaluation III (ODE III)
Reviewer Name(s)	Caren Kieswetter MD MPH
Review Completion Date	October 18, 2019
Established/Proper Name	Levonorgestrel (LNG)-releasing Intrauterine System (IUS)
Trade Name	Liletta
Applicant	Medicine360
Dosage Form(s)	IUS containing 52 mg LNG
Applicant Proposed Dosing Regimen(s)	Intrauterine insertion for up to 6 years
Applicant Proposed Indication(s)/Population(s)	Prevention of pregnancy Women of reproductive age
Recommendation on Regulatory Action	Approval of Efficacy Supplement S008 for NDA 206229 Liletta, to extend use of Liletta for prevention of pregnancy to up to six years. This recommendation is based on the Applicant's demonstration of an acceptable cumulative and Year-6 Pearl Index (PI) and an acceptable safety profile that has not changed significantly since the initial approval.
Recommended Indication(s)/Population(s) (if applicable)	N/A

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Glossary

AC	advisory committee
AE	adverse event
API	active pharmaceutical ingredient
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Council for Harmonization
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
LARC	long-acting reversible contraceptive
LNG IUS	levonorgestrel-releasing contraceptive intrauterine system
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event

NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PDMS	polydimethylsiloxane
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SHI	single-handed inserter device
SOC	standard of care
TEAE	treatment emergent adverse event
THI	two-handed inserter device

1. Executive Summary

1.1. Product Introduction

Liletta is a levonorgestrel-releasing contraceptive intrauterine system (LNG IUS), henceforth referred to by its trade name, Liletta, or IUS. It is a long-acting reversible contraceptive (LARC) initially approved by the FDA on February 26, 2015, for prevention of pregnancy for up to three years of use by parous and nulliparous women of any body weight.[1], [2] Medicines360 (M360), henceforth referred to as the Applicant, designed the Phase 3 multi-center open-label trial, L102, as an ongoing trial (b) (4) Liletta received FDA approval for extending duration of use up to four years on August 3, 2017, and up to five years on October 15, 2018. Currently, the Applicant seeks to extend duration of use up to six years with NDA Efficacy Supplement (ES) S008.

Liletta has three components: (1) the T-frame, (2) a drug reservoir containing 52 mg of (b) (4) LNG, and (3) an outer membrane cover. Liletta's LNG is combined with polydimethylsiloxane (PDMS) (b) (4) polyethylene T-frame. A PDMS membrane (b) (4) surrounds the reservoir. The T-frame is compounded with barium sulfate for radio-opacity. A polypropylene monofilament thread used for removal is attached through an eyelet at the base of the T-frame.

There are currently five intrauterine devices or systems (IUSs) approved in the US, including Liletta. Four of the five IUSs are LNG-releasing: Liletta 52 mg LNG, Mirena 52 mg LNG (NDA 21225, approved in 2000), Kyleena 19.5 mg LNG (NDA 208224, approved in 2016), and Skyla 13.5 LNG (NDA 203159, approved 2013). ParaGard (NDA 18680, approved in 1984) is non-hormonal, but contains copper, which contributes to its contraceptive effect. Mirena is approved for up to five years for contraception; it also has a secondary indication of treatment of heavy menstrual bleeding. Kyleena and Skyla are approved for contraception for up to five and three years, respectively. ParaGard is approved for up to ten years for contraception. Liletta has been marketed in the European Union since 2015 (commercial name Levosert®).

[1] Liletta, initially approved for use with a two-handed inserter (THI) device, received approval for use with a single-handed inserter (SHI-001) on January 29, 2016. The SHI-001 is the only inserter marketed and distributed since February 17, 2017.

[2] The Applicant had a Postmarket Study Commitment (PSC, #2874-1) from February 13, 2015, to characterize the frequency of specific outcomes for the THI-002 inserter and compare it to the SHI-001. This descriptive observational cohort study was to be completed on February 28, 2018. However, the Agency released M360 from this PSC on September 13, 2017, because the study was no longer feasible—the THI-002 inserter was no longer marketed or distributed and had been replaced by the SHI. No other postmarketing requirements or risk evaluation and mitigation strategies (REMS) were required for approval.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The Applicant has provided substantial evidence of effectiveness to support approval of Liletta for the prevention of pregnancy in females of reproductive potential for up to six years. The evidence of clinical efficacy derives from Study M360-L102 that shows an acceptable cumulative and Year 6 Pearl Index (0.18 and 0.00, respectively). This supports extending Liletta's duration of use to six years.

1.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

Unintended pregnancy affects millions of women in the United States annually and has far-reaching public health consequences. Therefore, safe and effective contraception is crucial to women's health. Development of contraceptive options with different modes of administration, more convenient dosing regimens, lower doses, and optimal efficacy and safety profiles remains a public health priority. A hormone-releasing IUS with demonstrated efficacy and safety for up to six years of pregnancy prevention adds a new option to available contraceptive products.

The Liletta IUS is a LNG-releasing LARC composed of a T frame (compounded with barium sulfate for radio-opacity), a drug reservoir containing 52 mg of (b) (4) LNG, and an outer membrane cover. Liletta was initially approved for up to three years of pregnancy prevention in February 2015. Liletta received FDA approval for extending duration of use up to four years in August 2017 (Efficacy Supplement 004), and up to five years in October 2018 (Efficacy Supplement 007). The Applicant now presents data to support approval for up to six years of use (Efficacy Supplement 008).

Substantial evidence of effectiveness for up to six years of use has been demonstrated in Trial M360-L102, an ongoing, prospective, multi-center, open-label, non-controlled Phase 3 trial. The Applicant submitted data demonstrating adequate efficacy based on evaluable cycles from the Phase 3 trial, enrolling a total safety population of 1,751 healthy women 16-45 years of age who were sexually active with regular menstrual cycles. The efficacy analysis is based on the modified Intent-To-Treat (mITT) population, comprising subjects 16 through 35 years of age at enrollment (n = 1,600) for whom the IUS was successfully placed and for whom there was at least one assessment of pregnancy status after placing the IUS (n = 1,545). Nine pregnancies occurred in subjects completing up to six years of use, with none occurring in the sixth year of use. The yearly and cumulative PIs are shown in the following table:

Table 1: Liletta Pearl Index Calculations: Yearly and Cumulative for Subjects 16-35 Years of Age (Modified Intent-To-Treat), n=1538, Excluding Cycles With Other Contraceptive Methods Used

Year(s) Of Use	1	2	3	4	5	6
Pregnancies On-treatment Yearly	2	4	1	1	1	0
Pregnancies On-treatment Cumulative	2	6	7	8	9	9
# of Subjects Completing Study Yearly	1276	1035	860	720	598	321
Yearly # of Cycles	17175	14205	11760	9891	8335	5091
Yearly PI (CI)	0.15 (0.02, 0.55)	0.37 (0.10, 0.94)	0.11 (0.00, 0.62)	0.13 (0.00, 0.73)	0.2 (0.00, 0.87)	0.00 (0.00, 0.94)
Cumulative # of Cycles	17175	31380	43140	53031	61366	66457
Cumulative PI (CI)	0.15 (0.02, 0.55)	0.25 (0.09, 0.54)	0.21 (0.08, 0.43)	0.20 (0.08, 0.39)	0.19 (0.09, 0.36)	0.18 (0.08, 0.33)

PI = Pearl Index = (# pregnancies / total # of menstrual cycles) X (13 menstrual cycles / year) X 100 women years
CI = Confidence Interval
Sources: 6-Year Clinical Study Report Section 10 (Figure 6) and Section 14.1 (Tables 10.1 and 10.3); and Statistics Reviewer Analysis

The yearly and cumulative PIs are sufficient to establish efficacy of the product for prevention of pregnancy for up to 6 years of use. Notably, for all PI calculations, the difference between the PI point estimate and the upper bound of the 95% confidence interval does not exceed the maximum limit of one unit (a criterion of the final study protocol for the Phase 3 trial). Benefits of the product include the convenience of the dosing regimen: the IUS is inserted once and is effective for 6 years without the need to obtain a replacement. In addition, the product provides effective contraception without exposing patients to the risks associated with ethinyl estradiol administration. This IUS releases low doses of LNG into the uterine cavity; pharmacokinetic data show a mean plasma LNG concentration = 93 ± 45 pg/mL after 6 years of use.

The safety profile of Liletta was evaluated using a safety database of all enrolled subjects who underwent placement of the IUS (n = 1,751, 16 through 45 years of age), regardless of age or procedure outcome. The safety profile of LNG is well-characterized. Safety information assessed for this efficacy supplement includes earlier DBRUP reviews of Trial L102 and subsequent cumulative data for key safety concerns, as follows:

- NDA safety data in the initial submission and prior to September 1, 2015, previously reviewed by Daniel Davis, MD.
- NDA safety data from September 1, 2015, through May 3, 2017, previously reviewed by Gerald Willett, MD. (Includes 120-Day Safety Update, PADERS 1-8, and IUS perforation reports from FDA's Adverse Event Reporting System.)
- NDA safety data from May 3, 2017, through February 26, 2018, previously reviewed by Caren Kieswetter, MD, MPH. (Includes 120-Day Safety Update, PADERS 9-12, and IUS perforation reports from FDA's Adverse Event Reporting System.)
- NDA safety data in the 6-Year Study Report [December 28, 2009, (first subject enrolled) through August 20, 2018, (last date of data accrual for 6-Year Study Report)] and corresponding 120-Day Safety Update (data accrual between August 20, 2018, through February 28, 2019).
- Post-marketing safety data from the Periodic Adverse Drug Experience Report (PADER 13, Reporting Period February 26, 2018, through February 25, 2019) submitted April 22, 2019, to the NDA.
- FDA's Adverse Event Reporting System (FAERS) reports on uterine perforations and one death with Liletta use.

There were no new deaths reported in the Year 6 Study Report of Trial L102 or 120-day Safety Update. One death has occurred to date in Trial L102, a suicide (Subject (b) (6)) that was reported in the initial NDA submission and reviewed at that time. Adverse events (AEs) of special interest include ectopic pregnancy, uterine perforation, and certain severe infections. For subjects completing Year 6 of use in Trial L102, incidence rates of overall adverse events, serious adverse events (SAEs), and adverse events leading to discontinuation of the investigational product (or to discontinuation from the study), were similar to those observed in subjects during the first five years of use. Sixteen life-threatening SAEs have been reported in 14 subjects through February 28, 2019 (the data accrual end-date of the 120-Day Safety Update for this Efficacy Supplement). Three of these 16 life-threatening SAEs were classified as IUS-related—all were ectopic pregnancies treated surgically (none occurring in the sixth-year of use). No perforations or IUS-related infections requiring hospitalization were reported during the sixth-year of use. SAEs reported during the sixth-year of use were assessed as unlikely to be associated with the IUS; these SAEs were left-lower-lobe pneumonia, esophageal achalasia, appendicitis requiring appendectomy, and diverticulitis. No new safety signals were identified in the following data sets: subjects who experienced SAEs or discontinued the IUS due to an AE, common AEs reported, or vital signs and laboratory assessments.

In conclusion, based on the above considerations, the benefits of Liletta, when used according to labeling, outweigh its risks for the prevention of pregnancy for use up to six years.

Benefit-Risk Dimensions		
Dimension	**Evidence and Uncertainties**	**Conclusions and Reasons**
Analysis of Condition	• Unintended pregnancy affects millions of women in the United States each year and has far-reaching public health consequences, including adverse maternal and child health outcomes, and social and economic costs at the family and state/national levels. • In 2011, 45% (or 2.8 million) of the 6.1 million pregnancies in the US were unintended. • The 68% of women at risk for unintended pregnancy who use contraception consistently and correctly during any given year account for only 5% of all unintended pregnancies. • The 18% of women at risk for unintended pregnancy who use contraceptives inconsistently or incorrectly account for 41% of all unintended pregnancies. • The 14% of women at risk for unintended pregnancy who do not use contraception at all or who have gaps of a month or more during the year account for 54% of all unintended pregnancies.	Safe and effective contraception is crucial to women's health. As many options as possible should be available. Therefore, developing contraceptive options that facilitate consistent and correct use by offering different modes of administration, more convenient dosing regimens, lower doses, and optimal efficacy and safety profiles remains a priority. An IUS with demonstrated efficacy and safety extending to six years of use adds a valuable option among available contraceptive products.
Current Treatment Options	• Currently approved contraceptive products for women available on the US market include oral tablets, a transdermal patch, a subdermal implant, depot injections, intravaginal rings, and IUSs. • There are five approved IUSs. Liletta and Mirena (NDA 21225) are both approved for up to 5 years of use and contain LNG 52 mg. ParaGard, a non-hormonal IUS, is approved up to 10 years of use.	Despite the broad range of available contraceptives, limited options in dosing intervals hinders consistent and correct use. Daily, weekly, or monthly dosing regimens have limited adherence and may be associated with problematic side effects (e.g., irregular bleeding and spotting). About a third of women at risk for unintended pregnancy use contraceptives

Benefit-Risk Dimensions		
Dimension	**Evidence and Uncertainties**	**Conclusions and Reasons**
		inconsistently or incorrectly, or do not use them. An IUS providing six years of effective pregnancy prevention offers a convenient option that facilitates consistent and correct use.
Benefit	Benefits of the Liletta IUS: • *Favorable findings* in Study L102 support approval. • A *well-characterized* drug substance (levonorgestrel) and device component (an integral part of the drug delivery system) comprise this product. • A *known and acceptable risk profile*. • *Efficacy* in the sixth year of use: Year 6 PI of 0.0 (95% CI 0.00, 0.94) and a Cumulative PI of 0.18 (95% CI 0.08, 0.33). • *Sustained efficacy* despite expected declines in levonorgestrel plasma concentrations shown by pharmacokinetic data. • *Convenient dosing* with six years of contraception after initial insertion.	An IUS providing six years of safe and effective contraception provides a beneficial option.

Benefit-Risk Dimensions		
Dimension	**Evidence and Uncertainties**	**Conclusions and Reasons**
Risk and Risk Management	• There was one death of a study subject due to suicide during the Liletta IUS clinical development program, reviewed with the initial NDA submission and determined to be unrelated to use of this product. • There was one death of a patient, reported by a clinician to FDA's Adverse Event Reporting System (FAERS), due to a severe infection shortly after Liletta insertion; reviewed and assessed to be associated with Liletta use. • Risks of Liletta IUS use include ectopic pregnancy, uterine perforation, and certain severe infections. • Serious adverse events (SAEs) during Year 6 of Study L102 included one left-lower-lobe pneumonia, one esophageal achalasia, one appendicitis/appendectomy, and one diverticulitis; none were considered related to the IUS. • Results provided in the Year 6 Clinical Study Report of Trial L102 and the 120-day Safety Update indicate no new risks or changes to the overall established safety profile of the product compared to other LNG-releasing IUSs.	No change in the known safety profile of the product was observed in the extension trial; current labeling (as revised and approved October 15, 2018) adequately reflects the known risks, including death.

1.4. Patient Experience Data

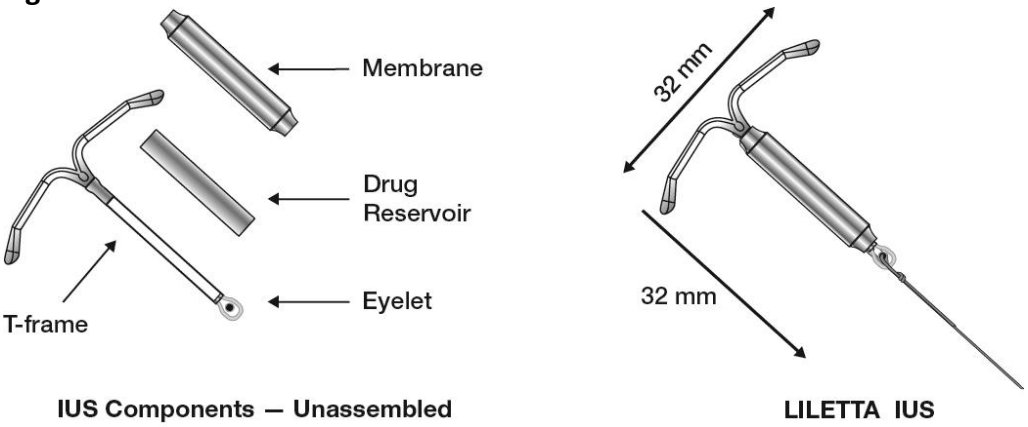
Patient Experience Data Relevant to this Application (check all that apply)

☐	The patient experience data that was submitted as part of the application include:			Section where discussed, if applicable
	☐	Clinical outcome assessment (COA) data, such as		[e.g., Sec 6.1 Study endpoints]
		☐	Patient reported outcome (PRO)	
		☐	Observer reported outcome (ObsRO)	
		☐	Clinician reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		[e.g., Sec 2.1 Analysis of Condition]
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify)		
☐	Patient experience data that were not submitted in the application, but were considered in this review:			
		☐	Input informed from participation in meetings with patient stakeholders	
		☐	Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Current Treatment Options]
		☐	Observational survey studies designed to capture patient experience data	
		☐	Other: (Please specify)	
☒	Patient experience data was not submitted as part of this application.			

2. Therapeutic Context

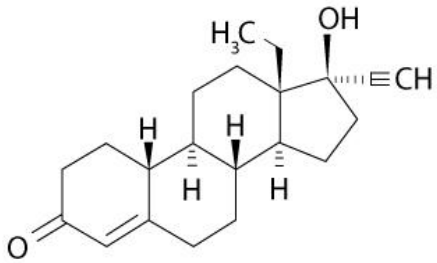
The Liletta IUS has three components: (1) the T-frame, (2) a drug reservoir containing 52 mg of (b) (4) LNG, and (3) an outer membrane cover. (Refer to the Prescribing Information.) The T-shaped polyethylene frame (T-frame) has the drug reservoir around the vertical stem (Figure 1). It has two horizontal arms at one end of the vertical stem and an eyelet loop at the other end. The drug reservoir consists of a cylinder, made of a mixture of 52 mg levonorgestrel and polydimethylsiloxane (PDMS) formed from silicone base, tetra-n-propyl silicate, and stannous octoate. The drug reservoir is covered by a translucent PDMS membrane. The low-density polyethylene of the T-frame is compounded with barium sulfate, which makes it radio-opaque. A blue polypropylene monofilament removal thread (which has a copper-containing pigment as a colorant) is attached to the eyelet loop. The components of Liletta, including its packaging, are manufactured without the use of natural rubber latex.

Figure 1: Liletta IUS



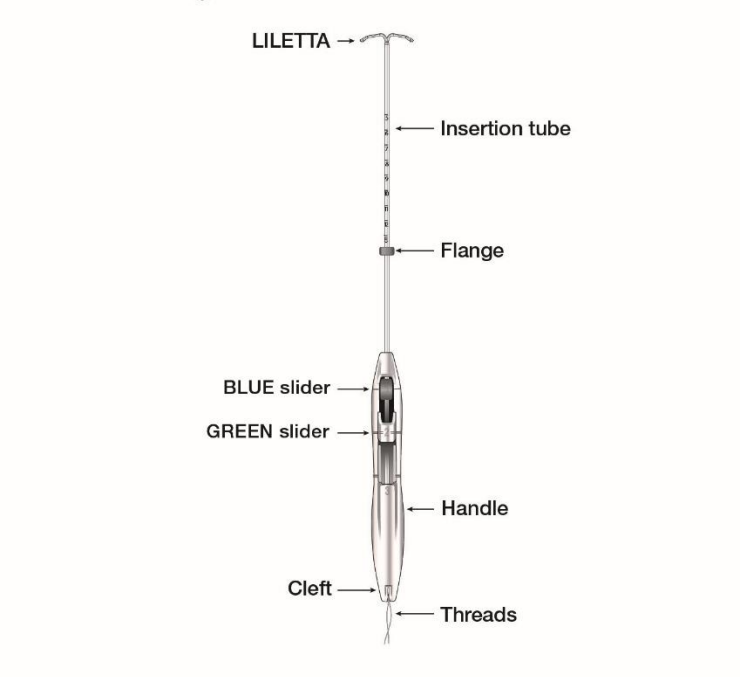
The active drug component in the Liletta IUS is 52 mg of LNG, intended to provide an initial release rate of 20(b) (4) mcg/day of LNG. This progestin, levonorgestrel USP (-)-13-ethyl-17-hydroxy-18,19-dinor-17α-pregn-4-en-20-yn-3-one, has a molecular weight of 312.45, a molecular formula of $C_{21}H_{28}O_2$, and the structural formula shown in the figure below.

Figure 2: Levonorgestrel Structural Formula



The inserter device provided with Liletta is a single-use, disposable, sterile insertion system (Figure 3), partially preloaded with the Liletta IUS for single-handed intrauterine administration.

Figure 3: Single-Handed Inserter for Liletta IUS



2.1. Analysis of Condition

Unintended pregnancy affects millions of women in the United States each year and has far-reaching public health consequences: adverse maternal-child health and social outcomes, and substantial economic burdens at family, state, and national levels.

In 2011, 45% (or 2.8 million) of the 6.1 million pregnancies in the US were unintended. Adolescents 15–19 years of age have the highest unintended pregnancy rate of any age-group (more than 600,000 per year), despite a declining pregnancy rate over the preceding two decades. Across population subgroups, unintended pregnancies also remain most common among women and girls who are poor and those who are cohabitating.

Consistent and correct use of contraception are important factors in preventing unintended pregnancies. The 68% of women at risk for unintended pregnancy who use contraception consistently and correctly during any given year account for only 5% of all unintended pregnancies. The 18% of women at risk for unintended pregnancy who use contraceptives inconsistently or incorrectly account for 41% of all unintended pregnancies. The 14% of women at risk for unintended pregnancy who do not use contraception at all or who have gaps of a month or more during the year account for 54% of all unintended pregnancies.

The Liletta hormone-releasing IUS, providing up to six years of effective pregnancy prevention, offers a convenient contraceptive option that further facilitates consistent and correct use. This product, like other LARCs, may have the greatest impact on reducing the 95% of unintended pregnancies that occur among women using contraceptives inconsistently or incorrectly, or not using contraceptives. As well, it may significantly reduce the high incidence of unintended pregnancies among adolescents—given current evidence about the successful use of LARC methods in this subgroup.

2.2. Analysis of Current Treatment Options

Currently approved contraceptive products for women available on the US market include oral tablets, a transdermal patch, a subdermal implant, depot injections, intravaginal rings, and intrauterine devices or systems (IUSs). Despite the broad range of available contraceptives, limited options in dosing intervals hinders consistent use. Daily, weekly, or monthly dosing regimens have limited adherence and may be associated with problematic side effects (e.g., irregular bleeding and spotting). LARCs, such as the hormone-releasing Liletta and Mirena IUSs, provide the option of a 5-year dosing interval.

Table 2 summarizes information about the five IUSs approved for use in the US, including Liletta. Four IUSs are LNG-releasing and one is non-hormonal (it contains copper, which contributes to its contraceptive effect). **Table 3** summarizes information about products containing LNG.

Table 2: Summary of Intrauterine Systems for Contraception* in the United States

Product	NDA #	US Approval Year	Duration of Use (Years)	Dose and Dimensions	LNG Release Rates**
Liletta (LNG) Current labeling shows reanalysis of release rates.	206-229	2015	5	52 mg LNG 32 mm Horizontal 32 mm Vertical	Initial ≈ 20.1 µg/day 1 Year ≈ 17.5 µg/day 2 Year ≈ 15.2 µg/day 3 Year ≈ 13.2 µg/day 4 Year ≈ 11.4 µg/day 5 Year ≈ 9.9 µg/day 6 Year ≈ 8.6 µg/day (b) (4)
Mirena* (LNG)	021-225	2000	5	52 mg LNG 32 mm Horizontal 32 mm Vertical	Initial ≈ 20 µg/day 5 Year ≈ 10 µg/day
Kyleena (LNG)	208-224	2016	5	19.5 mg LNG 28 mm Horizontal 30 mm Vertical	Initial ≈ 17.5 µg/day 5 Year ≈ 7.4 µg/day
Skyla (LNG)	203-159	2013	3	13.5 mg LNG 28 mm Horizontal 30 mm Vertical	Initial ≈ 14 µg/day 3 Year ≈ 5 µg/day
ParaGard T380A (Copper)	018-680	1984	10	380mm^2 Copper (exposed) 32 mm Horizontal 36 mm Vertical	N/A

* Mirena has approval for a secondary indication: treatment of heavy menstrual bleeding.
** Liletta's proposed labeling shows results from this reanalysis of release rates (over the 6-year period) that uses the expanded data set for analysis. The differences are minimal and not expected to have significant *in vivo* effect. Refer to the Biopharmaceutics Review by Jia Yin, PhD, September 8, 2019.
Source: Table adapted from NDA 206229 S004 Clinical Review, Gerald Willett, MD, June 28, 2017.

Table 3: Summary of Levonorgestrel-Containing Products

	Indication	Formulation/Route of Administration
LNG-Only	Emergency Contraception	• Oral
	Contraception	• Oral (not approved in US, e.g., Microlut, Microval, and Noregeston)
	Long-acting Reversible Contraception	• Intrauterine • Dermal Implant (approved in US, but marketed outside US)
	Heavy Menstrual Bleeding	• Intrauterine
LNG-Estrogen Combination	Contraception	• Oral
	Vasomotor Symptoms	• Oral
	Osteoporosis Prevention	• Oral

Source: Adapted from NDA 206229 S004 Clinical Review, Gerald Willett, MD, June 28, 2017.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Liletta was initially approved for prevention of pregnancy for up to three years of use on February 26, 2015. During pre-submission meetings and communications with the Agency, it was agreed that the Applicant would conduct a Phase 3 trial of at least 5-years duration and would seek initial approval of the IUS for three years-of-use; the Applicant would subsequently submit annual efficacy and safety data as efficacy supplements to support additional years of use (refer to details about these interactions in Section 3.2. of this review).

The insertion devices that have been used with the Liletta IUS during development and marketing were reviewed via consultation with the Center for Devices and Radiologic Health (CDRH). The Applicant initiated their Phase 3 trial with a two-handed inserter (THI-001) that was used on the initial approximately 700 subjects enrolled in the trial. Due to difficulties with insertion using the THI-001, the Applicant paused the study to develop a new single-handed inserter (SHI)—evaluated in a separate study to assess its function. The SHI was then used for the final approximately 900 subjects enrolled in the Phase 3 trial. For the initial NDA submission, the Applicant opted to market the IUS with a modified two-handed inserter (THI-002) due to their concerns about possible patent infringement. At the pre-NDA meeting held on September 17, 2013, the Division advised the Applicant to evaluate insertion outcomes with the THI-002 in a separate clinical study, and to submit analyses of safety and efficacy data stratified by the type of inserter used, as well as a pooled analysis. The clinical study evaluating the THI-002 was determined to be acceptable to support the overall safety and usability of the THI-002, with a successful insertion rate of 99% (95% successful on first insertion attempt). However, due to persistent difficulties with insertion and problems loading the inserter in some cases, a Postmarket Study Commitment (PSC, #2874-1) was established in February 13, 2015, to characterize the frequency of specific outcomes for the THI-002 inserter and compare it to the SHI-001. This descriptive observational cohort study was to be completed on February 28, 2018. However, the Agency released M360 from this PSC on September 13, 2017, because the study was no longer feasible—only the SHI-001 has been marketed and distributed since February 17, 2017, when marketing and distribution of the THI-002 ceased. (Refer to Section 12 of this review.) Liletta received approval for use with the SHI-001 on January 29, 2016, following review of ES S001.[3]

Liletta received FDA approval for extending duration of use up to four years (ES S004) on August 3, 2017, and up to five years (ES S007) on October 15, 2018.

[3]Efficacy Supplement S001 (SN0031), included safety data only, collected through September 1, 2015.

3.2.Summary of Presubmission/Submission Regulatory Activity

The Applicant conducted the drug development program for this indication under IND 105,836, opened on November 21, 2009.

Communication between the Applicant and the Agency related to this efficacy supplement included the following meetings:

- **September 10, 2009, Pre-IND Meeting:**
  - The Division agreed to the Applicant's plan to submit an initial NDA via the 505(b)(2) pathway, relying on published literature and FDA findings of safety for Mirena to support nonclinical safety of the product.
  - The Applicant stated they planned to conduct a Phase 3 trial to provide efficacy and safety data to support 5-7 years of use of the IUS, but they intended to submit an initial NDA to obtain approval for two years of use, with subsequent cumulative data submitted on an annual basis to support additional years of use.
  - The Division agreed to the Applicant's approach and clarified that if the product were approved, the indication and labeling would reflect the actual data that is submitted and reviewed (i.e., efficacy and safety data to support two years of use). The Division advised the Applicant that subsequent cumulative data could be submitted in efficacy supplement(s) to propose changing the indication to reflect a longer duration of use.
- **June 26, 2012, Type C Guidance Meeting:**
  - The Applicant reiterated their intention to submit an NDA to support an initial indication of two years of use, with a minimum of 200 women completing two years of drug exposure and a minimum of 10,000 cycles of cumulative exposure.
  - The Division agreed with this approach for evaluating efficacy for a two-year indication.
  - The Agency agreed that the initial LNG content of intrauterine system (IUS) units at lot release and the residual LNG content of expelled or removed IUS units can be used to determine the average in vivo release rate of LNG during the implant time interval.
- **September 17, 2013, Pre-NDA Meeting:**
  - The Applicant stated that they had collected a dataset of a minimum of 200 women who had completed three years of use of the product to submit to the NDA.
  - The Division stated that the Applicant's dataset appeared to be adequate to support an application for a three-year indication. The Division clarified that the Year 1, Year 2, and Year 3, and cumulative Pearl Indices would all be considered in evaluating efficacy of the product for a 3-year labeling indication.

The initial Liletta NDA with the indication of prevention of pregnancy for up to three years duration of use was submitted on April 29, 2014, and approval action was taken on February 26, 2015. ES S004 to extend duration of use to four years was submitted on October 3, 2016, and approval granted on August 3, 2017. ES S007 to extend duration of use to five years was submitted on December 15, 2017, and approval granted October 15, 2018.

3.3. Foreign Regulatory Actions and Marketing History

The Liletta IUS has been approved in more than 20 countries. It is marketed in the European Union, with the commercial name of Levosert, for contraception and management of heavy menstrual bleeding. In the United Kingdom, it received approval for extending duration of use to four years (in February 2018). At the time of Levosert's initial approval in the United Kingdom, the Medicines and Healthcare Products Regulatory Agency recommended a postmarketing study to evaluate performance of the THI-002, like the postmarketing study recommended by the FDA. There are no reports of adverse regulatory actions taken for Levosert by the EMA, to date.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

An audit by the Office of Scientific Investigations was not indicated.

4.2. Product Quality

The Chemistry Manufacturing and Controls (CMC) of LNG was adequate for approval in previous approval cycles and no changes have been made to the approved IUS. No new quality information was submitted for review with this Efficacy Supplement. The CMC review division does not request or require changes to the CMC portions of the label and recommends approval of this Efficacy Supplement. Refer to the CMC Review by Ramesh Gopalaswamy, PhD, September 26, 2019.

4.3. Clinical Microbiology

Not Applicable.

4.4. Nonclinical Pharmacology/Toxicology

The nonclinical information for LNG was adequate for approval in previous approval cycles and no changes have been made to the approved IUS. No new nonclinical information was

submitted for review with this Efficacy Supplement. The pharmacology/toxicology review team does not request or require additional nonclinical data to support extension of use to six years, has no nonclinical safety concerns, and recommends approval of this Efficacy Supplement. Refer to the Pharmacology/Toxicology Review by Miyun Tsai-Turton, PhD, MS, September 9, 2019.

4.5. Clinical Pharmacology

The clinical pharmacology data and analyses were adequate for approval in previous approval cycles and no changes have been made to the approved IUS. The Applicant updated the efficacy and safety data from the ongoing Trial L102 in this Efficacy Supplement (S008) to support the proposed extension of use through 6 years. The pharmacokinetic (PK) report and *ex vivo* LNG release data were updated through 7 years of use. Pharmacodynamic (PD) data (menstrual bleeding) were updated through 6 years of use. Exposure-response analyses for return-to-menses (RTM), return-to-fertility (RTF), and endometrial thickness (ET) were updated through 6 years of use. Key review topics and respective comments/recommendations by the clinical pharmacology review team are summarized as follows:

General Dosing Instructions:
The proposed dosing regimen is appropriate for the prevention of pregnancy for up to 6 years of use in the general population. Support for this conclusion include the following findings:

- The Applicant reported 9 on-treatment pregnancies occurred in the Liletta modified intention-to-treat (MITT) population through Year 6 of use: 2 in the first year, 4 in the second year, 1 in the third year, 1 in the fourth year, and 1 in the fifth year of use. According to the Applicant, no on-treatment pregnancy was reported in the sixth year of use and thus systemic exposure-efficacy analysis was not conducted in this Efficacy Supplement (S008).
- The Applicant updated bleeding and spotting data collected in Trial L102 (from summary questionnaires through subject interviews every 3 months) for up to 72 months. The bleeding and spotting data submitted in S004, S007, and S008 demonstrated a consistent bleeding pattern alteration following Liletta placement. Both the plasma PK profile and bleeding data indicated a sustained *in vivo* release LNG from Liletta.

Dosing Regimens for Subpopulations:
Subject age, body mass index (BMI)/body weight, race, and inserter type did not affect the efficacy of Liletta. No alternative dosing regimen or management strategy appears to be required for subpopulations. However, it is acknowledged that limited numbers of subjects in some of the trial's subgroups precludes definitive conclusions regarding dosing regimens and product effectiveness in subpopulations.

Labeling Revisions:
Revisions to the Prescriber Information (PI) reflect the expanded data set accrued over the 6-year period and changes in the number of subjects:

- Section 2.1: The release rate of LNG through 6 years of use.
- Section 12.3: The number of subjects for each race.

The Office of Clinical Pharmacology Division of Clinical Pharmacology-3 has reviewed the information contained in NDA 206229 S008 and recommends approval from a clinical pharmacology perspective. Refer to the Clinical Pharmacology Review by Peng Zou, PhD, September 10, 2019.

4.6. Devices and Companion Diagnostic Issues

The device component of this IUS is the SHI-001 inserter. This inserter was reviewed by CDRH during the 2016 review cycle. No changes have been made to the inserter and CDRH input was not necessary for the prior or current review cycles.

4.7. Consumer Study Reviews

Not Applicable.

5. Sources of Clinical Data and Review Strategy

5.1.Table of Clinical Studies

The Applicant conducted a single open-label Phase 3 pivotal trial (L102) to assess the efficacy, safety, tolerability, and continuation rates of Liletta. (Refer to **Table 4** below for the Trial L102 Summary.) Trial L102 was planned with an ongoing design to support multiple extensions of the duration of use—potentially up to ten years. It continues to be conducted in 30 sites within the US. Enrollment in L102 included sexually active women 16 to 45 years of age (n = 1751), regardless of parity, race, or BMI/weight; L102 began in **December 2009**.

Two different insertion devices were used to place Liletta during the trial. The original THI-001 inserter was used for the first 760 women enrolled in Trial L102. Trial enrollment was then suspended temporarily due to reports from investigators of difficult placements, placement failures, and the need for cervical dilation. The Applicant then developed the SHI-001 inserter that was used for the 991 women subsequently enrolled. Enrollment in Trial L102 was closed in **April 2013**.

The initial trial design included the Mirena® LNG-IUS as a comparator for European regulatory filing of Liletta. However, the Mirena arm was stopped after 159 subjects had been enrolled

because it was determined that available comparative safety data from Mirena was sufficient to evaluate Liletta. The EMA evaluated comparison data from a comparative menorrhagia study conducted in Europe, and from the Mirena prescribing instructions. From a clinical perspective, the limited Mirena data obtained from L102 would not support any substantive comparative conclusions regarding Liletta for labeling purposes.

Table 4: Liletta Phase 3 Pivotal Clinical Trial L102: Summary

Trial ID #s / Name Trial Sites Enrollment Periods	Trial Design	Trial Population	Subject Disposition	Treatment Duration	Trial Endpoints (EPs)
M360-L102 **NCT00995150** *A Phase 3, Multi-Center, Open-Label Study of a Levonorgestrel-Releasing Intrauterine System for Long-Term, Reversible Contraception*	Phase 3 Multi-Center Open-Label Ongoing Evaluation of Safety and Efficacy of LNG (52mg)-IUS in nulliparous or parous women desiring LARC	Women 16 to 45 years of age, sexually active, nulliparous (n = 1011) or parous (n = 740) Pediatric Subjects: Subset of Adolescents 16 -17 years of age → n = 11	**Enrolled**: Liletta n = **1751*** Mirena n = 159 Total n = 1910	≥ 85 months of use, with additional follow-up of 30 days after IUS removal.	Primary Efficacy EP: Pearl Index (PI) calculation of on-treatment pregnancy rate, excluding 28-day cycles with ≥ 1 day of concurrent use of another contraceptive, in the mITT group. Safety EPs: IUS Placement Adverse Events (AEs) AEs of Special Interest (AESIs): · Ectopic Pregnancy · Perforations · Expulsions · Infections (PID/Endometritis) · Ovarian Cysts Note: *A priori* subject subgroups were also analyzed for consistency of certain efficacy and safety findings: · Age · Parity · Race · BMI · Inserter Type
29 Active US Sites (30 US Sites total to date: Site 103 closed and Site 145 opened to follow subjects from Site 103 who wanted to continue)			Liletta **Efficacy Group** (16-35 years of age) n = **1600** 32 Failed Placement (2.0%) → n = 1568 Subset mITT Population → n = **1545****		
December 28, 2009 – July 2010 Using THI-001 760 Enrollees March 2012 – April 23, 2013 Using SHI-001 991 Enrollees			Liletta **Non-Efficacy Group** (36-45 yrs of age) n = **151** 5 Failed Placement (3.3%) → n = 146		

* Safety Analysis Population: All subjects enrolled who underwent the IUS placement procedure, regardless of age or outcome of procedure.
**Efficacy Analysis (Modified Intent-To-Treat, mITT) Population: All Liletta subjects 16-35 years of age at enrollment for whom the IUS was successfully placed and for whom there was at least one assessment of pregnancy status (pregnancy test) after placing the IUS.

5.2.Review Strategy

The review strategy for this Efficacy Supplement (S008), that aims to extend Liletta's duration of use from up to five years (per the currently approved indication) to up to six years, includes review of the following data sources and analyses of results from the Applicant:

Efficacy:

- NDA efficacy data for Trial L102 in the 6-Year Clinical Study Report [December 28, 2009 (date first subject enrolled), to August 20, 2018 (data cutoff date for 6-Year Clinical Study Report)], including Pregnancy Narratives.
- NDA Summary of Clinical Efficacy through August 20, 2018.
- Individual Efficacy Response Data: On-Study Pregnancies and All Pregnancies Reported (during follow-up in subjects who discontinued the IUS because they desired pregnancy).
- FDA's statistical assessment of the Applicant's analyses.

Safety:

- NDA safety data for Trial L102 in the **6-Year Clinical Study Report (December 28, 2009, through August 20, 2018), and the corresponding 120-Day Safety Update (August 20, 2018, through February 28, 2019)**.
- NDA Summary of Clinical Safety through August 20, 2018, and the corresponding Summary of Clinical Safety Amendment through February 28, 2019.
- Post-marketing safety data from Periodic Adverse Drug Experience Report (PADER) 13, submitted to the NDA since the last Efficacy Supplement (S007).
- Subpopulation safety data analysis pertaining to subjects who were adolescents at enrollment.
  Note: The initial Pediatric Study Plan of March 21, 2018, was submitted to the IND 105836.
- FDA's Adverse Event Reporting System (FAERS) reports on uterine perforations and one death case with Liletta use.
- Note: Protocol Amendments through the current Protocol Version 9.0, October 2, 2017, submitted to the IND 105836 (SN0122), were previously reviewed (refer to Clinical Reviews for the initial submission, S004, and S007).
- Note: NDA safety data in the initial submission and prior to September 1, 2015, was previously reviewed by Daniel Davis, MD. NDA safety data from September 1, 2015, through May 3, 2017, was previously reviewed by Gerald Willett, MD, (S004). NDA safety data from May 3, 2017, through February 26, 2018, was previously reviewed by Caren Kieswetter, MD, MPH, (S007).

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. Title of Study:

A Phase 3, Multi-Center, Open-Label Study of a Levonorgestrel-Releasing Intrauterine System for Long-Term, Reversible Contraception

6.1.1. Study Design

Overview and Objective

The L102 Phase 3 trial has an ongoing, prospective, multi-center, open-label design. (As noted previously, the initial trial design included a Mirena comparator arm. The Mirena arm was discontinued upon determination that sufficient comparative safety data were available from a prior study conducted in Europe, and approved Mirena labeling.) The trial objectives are summarized as follows:

Primary Objective:
To assess the contraceptive efficacy of the LNG-releasing IUS, Liletta, in nulliparous and parous women of child-bearing potential who desire long-acting reversible contraception.

Secondary Objectives:
To characterize and assess the following parameters:

- Safety, tolerability, bleeding patterns, and continuation rates of Liletta.
- Return of menses after discontinuation of Liletta.
- Return to fertility after discontinuation of Liletta.
- Plasma pharmacokinetics of LNG in a subset of subjects with serial sampling over the duration of use.
- Plasma LNG levels for all subjects starting with Month 36.
- Plasma LNG levels over the first 14 days following removal and completing the entire duration of use.
- Changes in endometrial thickness based on transvaginal ultrasonography at one year, five years, and eight years.
- Safety and tolerability of Liletta in cohort of women 36 - 45 years of age.
- Analysis of IUSs that are removed or expelled during the study.

Trial Design

As stated previously, Trial L102 has an ongoing, prospective, multi-center, open-label design.

Conduct of Trial:
Women 16 to 45 years of age provided written informed consent, underwent screening procedures, and enrolled in Trial L102 in accordance with protocol requirements. Non-emancipated subjects < 18 years of age required written parental consent for participation. Trial enrollment began on December 28, 2009, and was completed on April 23, 2013. An Independent Data Monitoring Committee (IDMC) was engaged to monitor subject safety and made recommendations regarding trial conduct.

Clinic **visits** were scheduled at Months 1, 3, 6, 12, 18, 24, 30, 36, 42, 48, 54, 60, 66, and 72. Additional visits are planned for Months 78, 84, 90, 96, 102, 108, 114, 120, and 121—consistent with the current Protocol Version 9.0 (extending duration of Trial L102 to 10 years) and included in the 6Y CSR. Clinic visits include the following assessments:

- High sensitivity urine pregnancy test.
- Examination for IUS string position.
- Collection of subject diaries for other contraception use.
- Subject interview regarding any changes in sexual partners, adverse events, or concomitant medications.

Refer to Table 5 to of this review for the complete Schedule of Events.

Additional subject **contacts** are made by phone every three months (in between clinic visits) to assess continued use of the IUS, changes in sexual partner, other contraceptive use, adverse events, concomitant medications, and bleeding and cramping/pain.

A safety follow-up visit is scheduled for all subjects 30 days after IUS discontinuation for final adverse event assessments and high-sensitivity urine pregnancy testing.

Ex vivo analysis is conducted on IUSs that are removed or expulsed to assess residual LNG content.

Subjects are separated into two cohorts to optimally characterize the efficacy and safety of the Liletta IUS. The **Efficacy Group** is comprised of women 16 to 35 years of age (n = 1600) to evaluate contraceptive efficacy. The **Non-Efficacy Group** is comprised of women 36-45 years of age (n = 151) to evaluate safety in older women who have decreased fecundity overall and more commonly choose intrauterine contraceptives. (Refer to Table 4 of this review for additional details about the trial analysis populations.)

Additionally, the following sub-analyses of the Efficacy Group were conducted at selected sites:

- LNG PK in non-obese vs. obese women through Month 30.
- Endometrial thickness in a subgroup of subjects by transvaginal ultrasound evaluations at baseline and Month 12.

Enrollment Criteria:
Enrollment criteria and medications not permitted during trial participation were based on sound rationales and are summarized as follows.

Key Inclusion Criteria:
- Healthy women, 16 to 45 years of age, inclusive. (Written parental consent required for subjects < 18 years of age.)
- Regularly sexually active in a mutually monogamous relationship for at least six months at study entry.
- History of regular menstrual cycles.

Key Exclusion Criteria:
- Currently pregnant or pregnant within four weeks prior to study entry.
- Currently breastfeeding.
- History of ectopic pregnancy without a subsequent intrauterine pregnancy.
- History of pelvic inflammatory disease without subsequent intrauterine pregnancy.
- Postpartum or post-abortion endometritis unless symptoms resolved at least four weeks prior to study entry.
- Current persistent, abnormal vaginal bleeding.

Excluded Medications:
- Hormonal contraceptives with the following exceptions:
  - An oral, transdermal, vaginal, or combined monthly injectable hormonal contraceptive during the first month of participation only.
  - Emergency contraception (EC) if subject felt the IUS expelled and she subsequently had intercourse. Subjects were not discontinued from the study after EC use.
- A previously inserted contraceptive implant, IUD, or IUS, unless it was removed prior to study IUS placement (removal immediately before study IUS placement was permissible).
- Any other contraceptive method that could confound the efficacy parameters of the Liletta IUS was not allowed during study participation. However, if the subject felt the need to protect herself against sexually transmitted infections, use of a male condom was allowed. If the use of a male condom became a regular part of the subject's contraception, the site Principal Investigator was required to contact the Medical Monitor about the possibility of discontinuing the subject from study participation. All condom usage was documented in the subject daily diaries.
- Any non-contraceptive estrogen, progesterone, testosterone, or gonadotropin.
- Misoprostol on day before or day of IUS placement or removal.
- Any cervical dilating instrument used during IUS placement other than Pratt dilators, a lacrimal duct probe, or an os finder.
- Any investigational treatment or medication other than the Liletta IUS.

Schedule of Events:
The trial Schedule of Events is summarized in **Table 5**. It incorporates changes made in the current Protocol Version 9.0, October 2, 2017. The key change in Protocol Version 9.0 is an extension of the trial period to study an extended IUS duration-of-use, from 8 years to 10 years (121 months). Additional assessments and analyses were added, accordingly.

Table 5: Liletta Clinical Trial L102: Schedule of Events for Trial Extension to 10 Years of Use

Assessments[1]	Enrollment	Visit	Contact	Visit	Visit	Visit	Visit	Contact	Visit	Contact	Visit	Term/Early Discontinuati	30 Day Safety FU	Continued Follow-up
	Day 1	Month 1, 3, 6, 18	Month 9, 15, 21	Month 12	Month 24	Month 36, 48, 72, 84, 96*†, 108*	Month 60	Month 27, 33, 39, 45, 51, 57, 63, 69, 75, 81, 87, 93, 99*, 105*, 111*	Month 30, 42, 54, 66, 78, 90, 102*, 114*	Month 93, 117*	Month 120*	Month 121*†	30-43 days	
Informed Consent	X													
Demographic Information	X													
Medical/Medication[2] History	X													
Breast Exam[3]	X			X	X	X	X				X	X[9]		
Vital Signs (wt, BP)	X	X		X	X	X	X		X		X	X	X	
Height	X													
Pelvic Exam with Pap	X[4]			X[4]	X[4]	X[4]	X[4]				X	X[4,9]		
Chlamydia/Gonorrhea	X[5,6]	X[6]		X[5,6]	X[5,6]	X[5,6]	X[5,6]		X[6]		X	X[5,6,7]	X[6]	
Urine Pregnancy	X[8]	X		X	X	X	X		X		X	X	X	
Hemoglobin	X			X			X				X	X[9]		
Serum Chemistry[10]	X													
Confirm Eligibility	X													
Assign IUS in IVRS	X													
Insertion of IUS	X													
AE Related to IUS Procedure	X											X		
Instruct/Dispense Daily Diary	X	X		X	X	X	X		X		X			
Counsel HIV/STD Risks	X													
Review Diary Compliance		X	X	X	X	X	X	X	X	X	X	X		
Bleeding/Cramping Form						X	X	X	X	X	X	X		
Review Contraception Use[11]	X	X	X	X	X	X	X	X	X	X	X	X	X	
Sexual Partner Status[6]		X	X[12]	X	X	X	X	X[12]	X	X[12]	X	X		
Review of Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	
Review Concomitant Meds		X	X	X	X	X	X	X	X	X	X	X	X	
Plasma Levonorgestrel						X††	X††		X††			X[9, 13]		
Verify IUS Presence[14]		X		X	X	X	X		X		X	X		
Ask About Relocation or Early Discontinuation Plans		X	X	X	X	X	X	X	X	X	X			
Removal of IUS												X		
Contraception Counseling			X[15]			X		X[15]		X[15]	X	X[16]	X	
Schedule/Confirm Next Visit	X	X	X	X	X	X	X	X	X	X	X	X	X	X[17, 18]

*LNG20 16-35 year old enrollment group only
[1] To occur ±14 days of clinic visit (±7 days for Months 1, 3 and 121)
[2] Medications for 7 days prior to enrollment and anticoagulants for 30 days
[3] Include any clinically indicated physical exam
[4] Pap test per protocol section 6.11 guidelines
[5] Chlamydia testing for all subjects ≤ 25 years old
[6] Both tests if change in sexual partner since last tested or last visit
[7] If not tested within the previous 6 months
[8] Urine pregnancy if not done on same day prior to insertion
[9] If not done within the last 3 months
[10] Includes creatinine, AST, ALT, bilirubin
[11] Review any other contraception use
[12] If change in sexual partner is noted during contact bring in for unscheduled G/C testing prior to next clinic visit
[13] Not required if Early Discontinuation <36 months
[14] By palpation or visualization (ultrasound evaluation if missing strings at first and annual visits)
[15] For contact or visit prior to Month 96 for LNG20 36-45 year old group and Month 121 for LNG20 16-35 year old group or Early Discontinuation discuss contraception options for discontinuation visit
[16] Initiation of primary method of contraception when possible
[17] Appropriate monthly contact by phone or clinic visit to follow ongoing AEs and return to menses. If no return to menses within 3 months of IUS removal/expulsion, refer for evaluation and continue follow-up until diagnosis is made
[18] For women desiring pregnancy follow by phone contact every 3 months up to one year based on date of IUS discontinuation
†LNG20 36-45 year old group see Month 121/ED procedures
†† LNG20 36-45 year old group only

Source: 6Y CSR Appendix 16.1.1 (Protocol Version 9.0, Appendix A)

Study Endpoints

Efficacy Supplement S008 limits efficacy evaluations of individual subjects to data obtained during the first six years of product use (72 months; 78 × 28-day cycles). However, Safety Evaluations, such as those for adverse events, include all data obtained through the data cutoff date. Secondary analyses include stratification of *a priori* subject subgroups (e.g., parity, race, BMI, and inserter type) to evaluate consistency of certain efficacy and safety findings. Refer to Table 4 of this review for a summary of trial endpoints.

Efficacy:
The primary efficacy endpoint for Trial L102 is contraceptive efficacy of Liletta based on the Pearl Index (PI) calculation of the on-treatment pregnancy rate using the following formula:

$$PI = (\#\text{pregnancies}/\text{total}\ \#\ \text{of menstrual cycles}) \times (13\ \text{menstrual cycles of exposure/year}) \times 100\ \text{women years}$$

Contraceptive efficacy of Liletta is determined in the mITT population [all Liletta subjects 16-35 years of age at enrollment for whom the IUS was successfully placed and for whom there was at least one assessment of pregnancy status (pregnancy test) after placing the IUS], excluding 28-day cycles with ≥ 1 day of concurrent use of another birth control method (BCM). As per the FDA request in the Pre-NDA meeting, the PI (primary outcome measure) is evaluated separately for each year, excluding cycles with use of other BCM.

Pregnancies occurring "on-treatment" are defined by protocol as those with reported dates of conception (confirmed by ultrasound examination when possible) during IUS use or up to and including 7 days after IUS discontinuation.

The secondary efficacy endpoints are listed below for reference, but will not be discussed further because they will not be used to support labeling claims for Efficacy Supplement (S008):

- PI Calculations:
  - mITT Population with no cycles excluded
  - Non-Efficacy Group (36-45 years of age)
  - Safety Group (All subjects with IUS placed, regardless of age/procedure outcome)
  - Ectopic Pregnancies
  - Inserter Type used
- Life Table Analyses:
  - Pregnancy Rate Overall
  - Age Group (< 18, 18-30, 31-35, 36-45, and 16-45 years of age)
  - Race (white and non-white)
  - Parity (nulliparous and parous)
  - BMI (≤ 24.9, 25.0-29.9, 30-39.9, ≥ 40 kg/m2)
  - Ectopic Pregnancies
  - Inserter Type

Safety:
The safety endpoints for Trial L102 are summarized as follows:

- Successful IUS Placement
- Adverse Events (AEs)
- AEs of Special Interest (AESIs):
    - Ectopic Pregnancy
    - Perforations
    - Expulsions
    - Infections (e.g., PID, Chlamydia, and gonorrhea)
    - Ovarian Cysts
- Pregnancy Outcomes
- Sign and Symptom Parameters (e.g., bleeding)
- Physical Examination Parameters (e.g., vital signs and pelvic/breast examinations)
- Continuation and Removal Rates
- Post-removal return-to-menses time intervals and fertility rates.

The incidence of all treatment-emergent adverse events (TEAEs), treatment-related adverse events (TRAEs), and serious adverse events (SAEs) are tabulated as a proportion of the number of subjects in the Safety Population. The incidence and duration of subject daily diary-reported bleeding and cramping are tabulated by 28-day cycle, 84-day interval, and 90-day interval of IUS use.

Statistical Analysis Plan

For Trial L102, the estimated number of subjects needed to evaluate the contraceptive efficacy of Liletta was based on the Pearl Index. Sample size was planned to achieve an acceptable Pearl Index through a minimum of eight years of use, assuming the following conditions:

- PI estimate < 0.280.
- The difference between the point estimate and the upper limit of the 95% confidence interval of the PI calculated for each year of use would not exceed 1 unit (based on peer-reviewed literature).
- Early discontinuations rates due to dropouts, IUS expulsions, pregnancies, and other reasons would not exceed 26% in Year 1, 19% in Year 2, 17% in Year 3, 10% in Years 4, 5, 6, 7, and 8; a cumulative total over eight years of **68%.**
- Loss of women-months for use in calculating the PI would not exceed 0.6 months per subject in Year 1 and 0.3 months per year in Years 2, 3, 4, 5, 6, 7, and 8.

Under these conditions, for the efficacy analysis it was expected that 1600 Liletta Efficacy Group subjects (16-35 years of age) would provide at least 10000 woman-months (28-day cycles) of exposure in the first two years with at least 200 subjects having at least two years of exposure, and that at least 500 women would remain on treatment through the end of eight years.

Extension of the trial period (from 8 years to 10 years, Protocol Version 9.0) required revising the expected sample size in anticipation of additional subject dropouts during the extended trial period:

- Early discontinuations rates due to dropouts, IUS expulsions, pregnancies, and other reasons would not exceed a rate not of 16% per year during years 4 – 10; a cumulative total discontinuation rate over 10 years of **76%**.

However, the key factor required for calculating the PI values is that a minimum of 200 women must complete each year of use in the trial. By August 20, 2018, an adequate number of 28-day cycles of use was available for appropriate calculation of the yearly Pearl Indices through Year 6 of use; i.e., there were 321 subjects in the mITT group completing at least six years of Liletta use in the trial.

The following populations were defined for analyses:

- *Safety Population (n=1751)*: All subjects enrolled who underwent the IUS placement procedure, regardless of age or outcome of the procedure. (The Efficacy Group and Non-Efficacy Group combined.)
- *Efficacy Group (n=1600):* Subjects who received Liletta and who were between the ages of 16 and 35 years, inclusive, at study enrollment. The primary efficacy endpoint was assessed on this group.
- *Modified Intent-To-Treat (mITT) Population*: A subset of the Efficacy Group: All subjects 16 - 35 years of age at study entry for whom the IUS was successfully placed in the uterus and for whom there was at least one report of pregnancy status (pregnancy test) after inserting the IUS. Notably, the mITT population included 11 (0.7%) adolescent subjects 16-17 years of age.
- *Per Protocol (PP)*: The subset of the mITT population with no major protocol deviations. Notably, no PP population analysis was conducted because only three of 1545 subjects (< 0.2%) in the mITT population had major protocol deviations that could impact the efficacy outcome (although none of these three subjects had an efficacy failure, i.e., pregnancy) and the PP population would be essentially indistinguishable from the mITT population.
- *Non-Efficacy Group (n=151):* Subjects who received Liletta and who were between the ages of 36 and 45 years, inclusive, at study enrollment. Safety in older women was evaluated in this group.

The following populations were defined for secondary analyses:

- *The Pharmacokinetics (PK) BMI Population*: All subjects enrolled in the BMI substudy and who had at least one post-placement PK assessment and no major protocol deviations.
- *The Endometrial Thickness (ET) Population*: All subjects enrolled in the ET substudy who had at least one post-placement ET measurement. Endometrial thickness measurements were obtained at baseline and Month 12 and Month 60, and are scheduled to be obtained after the full intended duration of use (Month 97).

For the primary PI outcome using exposure information for Year 1, Year 2, Year 3, Year 4, Year 5, and Year 6, the mITT population was used as the basis of exposure; 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.

Use of another birth control method within the first 28-day cycle following placement was not considered a basis for exclusion of that cycle since, per-protocol, the use of another birth control method was allowed as a back-up during the initial cycle following IUS placement.

The "on-treatment" pregnancy rate and its associated 95% confidence interval were also estimated using the Life Table method 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. Modified Life Table analyses were also conducted with exclusion of cycles in which another BCM was reported.

Life Table analysis was conducted on the following populations:

- mITT with no cycle exclusions for Year 1, Year 2, Year 3, Year 4, Year 5, and Year 6
- mITT subgroups (age, parity, race, BMI, and inserter type)

Protocol Amendments

There have been 9 versions of the protocol (8 amendments):

- Version 9, October 2, 2017
- Version 8, October 31, 2016
- Version 7, October 9, 2014
- Version 6, August 10, 2012
- Version 5, January 25, 2012
- Version 4, March 7, 2011
- Version 3, August 9, 2010
- Version 2, January 25, 2010
- Version 1, October 19, 2009

Protocol Versions 1-9 and corresponding summary of changes are provided in the 6Y CSR, Appendix 16.1.1; they were all previously reviewed.

6.1.2. Study Results

Compliance with Good Clinical Practices

The Certification of Compliance with Requirements of Clinical Trials (OMB Form FDA 3674) is completed, signed, and submitted with this Efficacy Supplement. Accordingly, the Applicant attests the pivotal Phase 3 clinical trial, L102, is conducted in compliance with Good Clinical Practice (GCP). This includes compliance with the CFR governing the protection of human subjects (21 CFR Part 50), Institutional Review Boards (21 CFR Part 56), and the obligations of clinical investigators (21 CFR 312.50 to 312.70). It is also conducted in compliance with the "Declaration of Helsinki" (as amended in Tokyo, Venice, Hong Kong, South Africa, and Edinburgh, and clarified in Washington and Tokyo), the International Conference on Harmonization (ICH) guidelines, and FDA regulations.

The protocol, informed consent document, and Investigator' Brochure for L102 were submitted to the Institutional Review Board (IRB) for each respective investigative site. The protocol and informed consent document received written approval from the IRBs, in accordance with current Food and Drug Administration (FDA) and local regulations, prior to any subject providing voluntary informed consent or enrolling in the trial. As noted, informed consent was also obtained and documented from a parent or legal guardian of non-emancipated subjects under 18 years of age. Provisions are made to repeat the informed consent process if required by an IRB for protocol amendments or if significant safety information becomes evident during the trial. Refer to the 6Y CSR, Section 5 (Ethics), for details.

The Applicant and its representatives ensure adherence to the investigational plan and GCP/ICH requirements by regular contact with the investigation sites through telephone communication, email correspondence, and on-site visits.

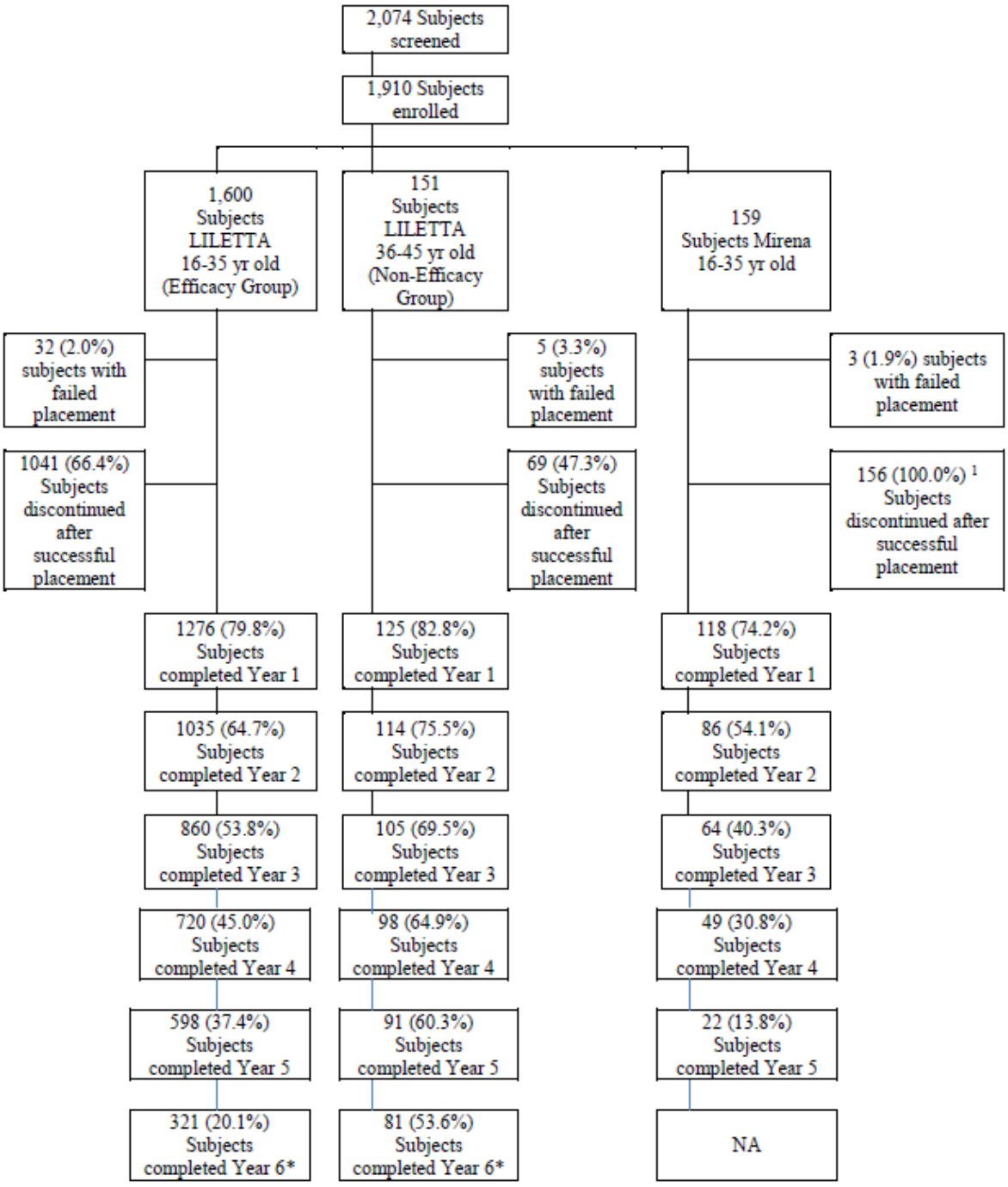
Financial Disclosure

The Certification of Financial Interests and Arrangements of Clinical Investigators (DHHS Form FDA 3454) is completed, signed, and submitted with this Efficacy Supplement. An appended list of investigator names is included, identifying 65 new investigators who have been added to the study since the submission of SN0000, SN0052, and SN0079. Checkbox (1) is marked on Form 3454 indicating that none of the investigators entered into any financial arrangement whereby the value of compensation could be affected by the outcome of the study or received significant payments of other sorts as defined in 21 CFR 54.2(f). Existing investigators made no changes to their respective financial disclosures.

Patient Disposition

Subject disposition in the 6Y CSR (S008) is summarized in Figure 4 below.

Figure 4: Liletta Trial L102: Disposition of Subjects* (Through August 20, 2018)**



* In this algorithm Years of Use is computed based on cycles of use (13 cycles/year), in lieu of days of use = [(30.4 days/month) X 60months]-14days.
**All active subjects have completed year 5, not all have completed year 6, some have started year 9.
Source: 6-Year Clinical Study Report (S008) Section 10, Figure 6, p85/249, and p86/249.

Cumulative discontinuations among subjects with successful IUS placement, through the 120-Day Safety Update for S008, are summarized in **Table 6** below. Frequency of reasons for discontinuation are consistent with those from previous datasets. The most frequent reasons for subject discontinuations include adverse events (excluding expulsions), desired pregnancy, lost to follow-up, and subject relocation. The 120-Day Safety Update for S008 provides additional information about subject discontinuations for the time interval between August 20, 2018, through February 28, 2019. Compared to the to the August 20, 2018, data set, there were 48 additional subject discontinuations: 1 completed full protocol, 15 desired pregnancy, 1 had an expulsion, 4 (8%) had other AEs, 2 withdrew consent, 6 were lost to follow-up, and 20 (42%) discontinued for other reasons. There were no new perforations.

Table 6: Liletta Trial L102: Subject Discontinuations Cumulative (Through February 28, 2019)

Reason for Discontinuation	Liletta Safety Population		
	16-35 Years of Age N=1600 [n (%)]	36-45 Years of Age N=151 [n (%)]	Total N=1751 [n (%)]
Completed Full Protocol†	0	46 (31.5)	46 (2.7)
Desired Pregnancy	276 (17.6)	4 (2.7)	280 (16.3)
Pregnancy with IUS in Place	1 (0.1)	0	1 (0.1)
Expulsion of IUS (Complete or Partial)	62 (4.0)	7 (4.8)	69 (4.0)
Adverse Event (Excluding Expulsions)*	241 (15.4)	23 (15.8)	264 (15.4)
IUS Not 1° Contraceptive	20 (1.3)	0	20 (1.2)
Subject Relocation	107 (6.8)	4 (2.7)	111 (6.5)
Consent Withdrawn	54 (3.4)	4 (2.7)	58 (3.4)
Lost to Follow-Up	190 (12.1)	19 (13.0)	209 (12.2)
Applicant Decision**	5 (0.3)	0	5 (0.3)
Investigator Decision***	13 (0.8)	2 (1.4)	15 (0.9)
Other†† (not including Subject 130-2010 erroneously reported as discontinuing due to AE)	205 (13.1)	19 (13.0)	224 (13.1)
Total Discontinuations	1174 (74.9)	128 (87.7)	1302 (76) †††

* There were 4 new discontinuations due to AEs, but only 3 new AEs because one subject (b) (6)) withdrew due to a previously reported AE (vaginitis bacterial).

** Includes poor mental health (3), entry into drug addiction rehabilitation (1), or work outside the country for extended period (1). All previously reported.

*** Includes non-compliance (10), substance abuse (1), poor mental health (1), illness (1), or use of an excluded therapy (1). All previously reported.

† A higher proportion of subjects completed full protocol in 6Y (n=40) vs 5Y (n=6).

†† Includes subject desire for a different contraceptive method (28), reduced menstrual suppression over time (17), desire to end study commitment at protocol duration-of-use (13 at 5Y and 6 at 7Y), or having no specified reason (64).

††† Discontinuations between the 120-Day Safety Updates for S007 and S008 (~1 year): 143 of 1302.

Sources: Adapted from 6Y CSR for S008, Section 10, Table 4 and narrative, pp89-90/257;
and 120-Day Safety Update for S008, Section 2.7.4.1.3.a, Table 2, pp6-7/54.

Protocol Violations/Deviations

Protocol deviations are reported when recognized by the site and following data review from regular site monitoring visits. Sites are required to submit all protocol deviations to their

governing IRB per their respective requirements. A total of 4891 protocol deviations were reported by the data lock cutoff date for the 6Y CSR (359 deviations since the 5Y CSR), an average of about 2.6 deviations per subject enrolled, with all ongoing subjects having completed at least 5 years of study participation. **Table 7** summarizes reported protocol deviations.

Table 7: Liletta Trial L102: Protocol Deviations Reported

Protocol Deviation Category	N	Description
Consent	374	Informed Consent Form, HIPAA, etc.
Inclusion Criteria	5	3 Criterion #2: Not healthy 2 Criterion #5: Irregular Menses
Exclusion Criteria	22	8 Criterion #12: Documented acceptable Pap ≤ 18 months 5 Criterion #2: Medical Abortion < 4 weeks; 5 Criterion #9: Active cervical infection 1 Criterion #1: Currently pregnant 1 Criterion #20: Drug abuse 1 Criterion #22: DMPA < 9 months 1 Criterion #27: Major depressive disorder
PK BMI Entry Criteria	1	Inadequate Washout
IUS Placement Timing	30	Not inserted in first 7 days of cycle, etc.
Lab	751	Failure to Collect, Incorrect Lab Collected, etc.
Out-of-Window Missed Visits	3278	2354 Out-of-Window 924 Missed Visits
Visit Procedures	376	Missed Exams, Lab Collection, Delayed SAE Reporting, etc.
Excluded Concomitant Treatment	36	Hormone Use (systemic, topical, hCG-diet) Condom Use Experimental Therapy (vaccine, gabapentin, bariatric therapy
Study Drug	18	IUS not returned upon removal IUS improperly stored upon removal Inserter not retained

Source: Adapted from 6Y CSR for S008, Section 10.1., Table 5, p95/257

The most frequently reported deviations are related to out-of-window (2354) or missed (924) visits/contacts, representing two-thirds (67%) of all deviations. Notably, the 235 subjects classified as lost to follow-up had to miss at least two consecutive study visits/contacts to be considered lost to follow-up. Therefore, the lost to follow-up subjects accounted for at least 470 (51%) of the missed visits/contacts (470 of 924)—about 10% of protocol deviations overall.

Informed consent was obtained from all subjects prior to any study procedures, including documentation of the consent process. The 374 consent-related deviations are primarily due to failure to obtain consent again at the visit following revision of the Informed Consent Form (ICF) or errors in completing the ICF or HIPAA form (e.g., failure to check all required boxes, appropriately complete signature and date lines, or adequately document corrections).

One deviation pertained to Exclusion Criterion #1 prohibiting enrollment while pregnant. Subject (b) (6) was pregnant when she was inadvertently enrolled through the Interactive

Voice Response System (IVRS), but never had an IUS placement attempt because the investigator received the affirmative pregnancy test result prior to attempting placement. This subject was withdrawn from the study.

Four subjects had SAEs that were inadvertently not reported to the Applicant within 24 hours of the site becoming aware of them (none were expedited cases and three were previously reported): Subject (b) (6) Cholecystitis, Subject (b) (6) Bipolar Disorder, Subject (b) (6) Acute Polyarthralgia and Myalgia, and Subject (b) (6) Portal Vein Thrombosis and Splenic Hamartoma).

For the PP population, major protocol deviations that could potentially affect the primary efficacy endpoint were identified prior to database cut-off: Inclusion Criterion #5, Exclusion Criteria #1, #4, #5, #6, #7, #11, #15, #21, #22, #23, and "Excluded Concomitant Medications". As noted in the Section pertaining to the Statistical Analysis Plan in this review, only three of 1545 subjects (< 0.2%) in the mITT population had major protocol deviations that could impact the efficacy outcome (two did not meet Inclusion Criterion #5 requiring regular menstrual cycles and one met Exclusion Criterion #22 prohibiting the use of DMPA injection within nine months prior to enrollment). None of these three subjects had an efficacy failure, i.e., pregnancy. Therefore, the Applicant decided to forgo separate PP population analyses because the PP population would be essentially indistinguishable from the mITT population.

The Applicant uses reasonable and effective management strategies to address and mitigate protocol violations, as indicated by the decreasing frequency of protocol violations over the course of Trial L102. The Applicant states that personnel undergo extensive, continuous training to implement protocol amendments and corrective actions based on site visit findings. Upon enrollment, subjects received the Informed Consent Form (ICF) that outlines their responsibilities and the expected study visit and contact schedule; updates to the ICF are provided to subjects as they occur. Sites were trained to establish routine advance reminders of upcoming study visits to minimize out-of-window or missing visits.

Table of Demographic Characteristics

The demographic characteristics of the study population are unchanged from the original NDA and are summarized in **Table 8** below. Demographic characteristics of the total Safety population are comparable to those of the mITT population. The main differences are due to inclusion of the older women (36-45 years of age) in the total Safety population. Refer to Table 4 ("Subject Disposition" column) of this review for a summary of the composition of study groups.

Demographic variables assessed in Trial L102 include age, ethnicity, race, marital status, partner cohabitation status, height, weight, BMI, medical history, gynecologic history, menstrual history, and pregnancy history. These variables were similarly assessed for the THI vs SHI and PK-BMI sub-studies. The distribution of ethnicity and race approach the demographic

composition of the US population at the time of subject recruitment (but may not reflect the demographic composition of US women likely to use the IUS method of contraception—as the Applicant intended). The following Cross-Discipline Team Leader comments from the review of the initial NDA (refer to the CDTL Review of February 25, 2015) are noteworthy:

- *"The proportion of Caucasians is slightly higher than that in the general US population, but race/ethnicity is not expected to impact the IUS's safety or efficacy.*
- *The study included a good representation of nulliparae, which should be sufficient to allow evaluation of safety and efficacy in this subgroup.*
- *The study was very successful in enrolling women of higher BMI…."*

Table 8: Liletta Trial L102: Demographic and Baseline Characteristics of Safety Populations*

Demographic Parameters	16-35 Years Efficacy Group (N=1600)	36-45 Years Non-Efficacy Group (N=151)	Total Safety Population (N=1751)
Age (Years)			
Mean (SD)	26.2 (4.4)	39.6 (2.7)	27.3 (5.7)
Median	26	39	26
Ethnicity [N (%)]			
Hispanic or Latina	237 (14.8)	21 (13.9)	258 (14.7)
Race [N (%)]			
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	1,250 (78.3)	120 (79.5)	1,370 (78.4)
Multiple Races Indicated	49 (3.1)	1 (0.7)	50 (2.9)
BMI (kg/m^2)			
N	1,596	151	1,747
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** [N (%)] → Overweight	390 (24.4)	37 (24.5)	427 (24.4)
BMI ≥ **30** [N (%)] → Obese	383 (24.0)	55 (36.4)	438 (25.1)
BMI ≥ **40** [N (%)] → Morbidly Obese	79 (4.9)	14 (9.3)	93 (5.3)
Weight (lbs)			
Median	148	158	--
Min - Max	83 - 380	94 - 381	83 - 381
Nulliparous [N (%)]	989 (61.8)	22 (14.6)	1,011 (57.7)
Age (Years)			
Mean (SD)	24.8 (3.8)	38.7 (3.0)	25.1 (4.3)
Median	24	38	25
Parous [N (%)]	611 (38.2)	129 (85.4)	740 (42.3)
Age (Years)			
Mean (SD)	28.3 (4.5)	39.8 (2.6)	27.6 (4.6)
Median	29	39	30
Partner Status [N (%)]			
Lives With Partner	915 (57.2)	106 (70.2)	1,021 (58.3)
Does Not Live With Partner	685 (42.8)	45 (29.8)	730 (41.7)

* At the time enrollment closed, April 23, 2009.
Source: Adapted from 6Y CSR for S008, Section 11.2., Table 8, pp99-100/257 (Consolidated from Section 14.1, Tables 2.1, 2.1.3, and 2.1.4).

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Table 9 below summarizes selected characteristics of gynecologic history for the mITT population.

Table 9: Liletta Trial L102: Gynecologic History of mITT Population at Close of Enrollment

Gynecologic Characteristic at Baseline	16-35 Years of Age (N=1545)
Sexually Transmitted Infection History [N (%)]:	
Pelvic Inflammatory Disease	6 (0.4)
Chlamydia	178 (11.5)
Gonorrhea	39 (2.5)
Selected Gynecologic Surgery [N (%)]:	
Uterine Surgery Unrelated to Pregnancy	1 (0.1)
Hysteroscopy with Polypectomy	0
Other	1 (0.1)
Baseline Method of Birth Control [N (%)]:	
None	141 (9.1)
Combination Oral Contraceptive	466 (30.2)
Progestin-Only Oral Contraceptive	32 (2.1)
Vaginal Ring	127 (8.2)
Transdermal Contraceptive	9 (0.6)
Progestin Implant	9 (0.6)
Condom Alone	498 (32.2)
Condom with Spermicide	51 (3.3)
Spermicide Alone	5 (0.3)
Diaphragm	1 (0.1)
LNG IUS	109 (7.1)
Copper IUD	23 (1.5)
Natural Family Planning	10 (0.6)
Withdrawal	56 (3.6)
Other	8 (0.5)

Source: Adapted from 6Y CSR for S008, Section 11.3.1., Table 10, p101/257 (Section 14.1, Table 3.2).

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment compliance is monitored during scheduled visits and contacts (refer to Table 5 of this review). Monitoring procedures include assessments of the following key variables: diary completion (e.g., any other contraceptive use, sexual partner status, and concomitant medications); IUS presence; potential subject relocation or plan for early discontinuation; and plan for subsequent visit. Table 6 and Table 7 of this review (pertaining to subject discontinuations and protocol deviations, respectively) include details about treatment compliance.

A history of medication use for 7 days (and anticoagulant use for 30 days) prior to enrollment was obtained at screening. Concomitant medications include any prescription medications or over the counter preparations taken during the study period. They were reviewed at the IUS placement attempt visit and also during study participation (each site visit and contact).

The Applicant provides tabulations showing limited use of pre-trial and concomitant medications. Concomitant or back up contraceptive use is summarized as follows:

- All reported levonorgestrel use in this study was as allowed per the protocol.
    - For levonorgestrel being reported as a concomitant medication in 200 Liletta subjects (11.4% of the full Safety Population), all but three cases (all in the Efficacy Group) involved subjects who were *completing* prior contraceptive therapy [e.g., an oral contraceptive pill pack or a prior Mirena IUS up to time of the placement of the study IUS (removing prior IUS and starting study IUS in the same visit was allowed per protocol)], or *starting* a levonorgestrel IUS following discontinuation of the study IUS.
    - Three subjects ([redacted] (b) (6)) reported use of emergency contraception (Plan B; allowed per protocol).
- Similarly, the other contraceptives listed as concomitant medications (e.g., Cilest, Eugynon) were used during the first cycle after IUS placement and represent subjects *completing* their prior contraceptive therapy per protocol or *starting* a new contraceptive method following discontinuation (through 30 days) of the study IUS.

Efficacy Results – Primary Endpoint

Contraceptive efficacy of Liletta is based on the on-treatment pregnancy rate assessed using Pearl Index (PI) calculations and Life Table analyses. Pregnancy is defined as a positive blood or urine pregnancy test. As noted, pregnancies occurring "on-treatment" are defined per protocol as those with reported dates of conception (confirmed by ultrasound examination when possible) during IUS use or up to and including 7 days after IUS discontinuation. The Applicant assesses on-treatment pregnancies accordingly; no discrepancies are identified. Pregnancies occurring on-treatment with Liletta are summarized with respective narratives in **Table 10**.

Table 10: Liletta Trial L102: Pregnancies On-Treatment (Through February 28, 2019)

Pregnancies On-Treatment with Liletta LNG-Releasing IUS			
Subject ID Age (Years)*	**Exposure Year (Months Post-Insertion)**	**Parity****	**Outcome**
(b) (6) 35	Year **1** (8 months)	P	**Ectopic pregnancy** treated with open salpingectomy during which IUS was not found. On a subsequent laparotomy, IUS removed from the abdominal cavity. Therefore, a ***perforation*** is presumed.
(b) (6) 27	Year **1** (9 months)	P	**Intrauterine pregnancy.** IUS not visible on ultrasound. The subject declined further imaging to locate the IUS until after the pregnancy. She delivered a healthy baby at 38 weeks. A postpartum radiographic examination determined that the IUS had not perforated. In the opinion of the Investigator this case represented a pregnancy with an unrecognized ***expulsion*** of the IUS.
(b) (6) 24	Year **2** (13 months)	P	**Anembryonic gestation.** IUS visualized in the uterus. Positive hCG. Vaginal ultrasound found intrauterine pregnancy with gestational sac but no embryo; hemorrhagic material surrounding the gestational sac and subchorionic hematoma noted. IUS removed.
(b) (6) 30	Year **2** (21 months)	P	**Ectopic pregnancy** treated with salpingectomy. At initial pregnancy evaluation ultrasound visualized IUS in the uterus.
(b) (6) 21	Year **2** (15 months)	NP	**Ectopic pregnancy** presumptively diagnosed and subject taken to OR. The IUS was intrauterine. Laparoscopy found hemoperitoneum with no masses visible in fallopian tubes, but a hemorrhagic nidus on the ovary. Pathology of peritoneal fluid identified chorionic villi. Patient treated with methotrexate and diagnosed with concomitant ruptured ovarian cyst. IUS removed several months postop.
(b) (6) 25	Year **2** (21 months)	NP	**Ectopic pregnancy** treated with methotrexate. Ultrasound visualized IUS in the uterus. IUS removed.
(b) (6) 26	Year **3** (24.9 months)	NP	**Ectopic pregnancy** treated with methotrexate.
(b) (6) 18	Year **4** (39 months)	P	**Ectopic pregnancy** treated with methotrexate***. IUS in low lying position in the cervix***.
(b) (6) 24	Year **5**		**Early pregnancy failure.** The narrative indicates a short-lived "chemical pregnancy" in a subject who was noncompliant with evaluation.
(b) (6)	Year 7*** (75 months)		**Intrauterine pregnancy.** IUS removed (b) (6) because subject desired pregnancy; she did not use contraception after IUS removal. At 30-day safety follow-up on (b) (6) had positive hCG. Three ultrasounds were consistent with date of conception on (b) (6), which is <7 days after IUS removal. This meets study criterion for product failure.
(b) (6) 21	Year 7*** (79 months)	NP	**Ectopic pregnancy** treated with salpingectomy. Initial evaluation with transvaginal ultrasound identified IUS in the uterus. IUS removed at the time of salpingectomy. Subject subsequently experienced Serious Adverse Event of **post-appendectomy intraabdominal abscess** (dates and details not provided); assessed as not-related to IUS or IUS procedure, Applicant concurred.

* Subject Age at Enrollment
** NP=Nulliparous and P=Parous
*** Year 7 on-treatment pregnancies included for completion of data provided to date by Applicant.
Source: Adapted from 6Y CSR for S008, Appendix 16.2.6, Listing 14 *On-Treatment Pregnancies Reported* and Listing 34 *All On-Study Pregnancies Reported (Including Pregnancies in Subjects Who Discontinued IUS Treatment Because Pregnancy Desired)*.

Nine on-treatment pregnancies have occurred in subjects who completed up to five years of Liletta use (all previously reported). None have occurred among subjects during the sixth year of use, through February 28, 2019. Of the nine on-treatment pregnancies, six were ectopic, one was anembryonic, one presented as an early pregnancy failure, and one was an intrauterine pregnancy (IUP) that progressed to full term. Six of these nine on-treatment pregnancies appear to have occurred with normal placement of the IUS within the uterus; however, one was consistent with a perforation, one with an expulsion (the IUP), and one could not be evaluated. These findings are consistent with those reported in the literature.

Note that Table 10 includes two additional pregnancies that occurred beyond six years of use; accordingly, they are not included in the Year-6 PI calculation.

The primary efficacy results are based on the Pearl Index and Life Table methods of analysis for the **mITT population** (N=1545, women **16-35 years of age** with successful IUS placement and at least one subsequent assessment of pregnancy status), excluding cycles during which other BCMs were used. Efficacy is predominantly determined by the overall acceptability of the PI and not only on the precision of the estimate. Acceptable precision of the PI is defined as having an upper bound of the 95% CI that is no greater than 1 unit from the point estimate of the PI.

The Applicant also provides efficacy results based on Life Table analysis. This shows cumulative rates of pregnancy at the end of the study, and at the end of each preceding cycle. The Life Table approach does not typically exclude individual cycles for a given subject, such as a cycle in which an alternate method of birth control was used. (By definition, this approach censors a subject from the remainder of the trial as soon as she uses back-up contraception, or includes all cycles without regard to use of back-up contraception.) For this reason, this type of analysis is often not directly comparable to the Pearl Index.

The Applicant performed Life Table analyses that (by definition) do not exclude cycles with back-up contraception. Additionally, the Applicant conducted modified Life Table analyses using a “continuous cycle” data construct that excluded these cycles. Using this data construct, the absolute number of complete 28-day cycles is adjusted downward for cycles with back-up contraception use reported. This allows inclusion of cycles subsequent to the ones with back-up contraception use.

A minimum of 10,000 evaluable cycles of exposure occurred in the first year of use and a minimum of 200 subjects have completed each year of use evaluated, as requested by the Division. No PP population analysis results are presented because only 3 subjects had major protocol deviations that excluded them from the mITT population. The primary efficacy results for S008 are based on the data submitted using the cutoff date of August 20, 2018.

Table 11 presents the **yearly PI** results for the mITT population reported in the 6Y CSR. There were 2 on-treatment pregnancies in the first year; 4 additional on-treatment pregnancies in the

second year; and one additional on-treatment pregnancy in the third, fourth, and fifth years in the mITT population. The pregnancy rates, as calculated by the PIs and associated 95% confidence intervals (CI), in the Liletta mITT population are 0.15 (95% CI: 0.02, 0.55), 0.37 (95% CI: 0.10, 0.94), 0.11 (95% CI: 0.00, 0.62), 0.13 (95% CI: 0.00, 0.73), 0.16 (95% CI: 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 **cumulative PI** from Year 1 to Year 6 is 0.18 (95% CI: 0.08, 0.33), as shown in **Table 12**.

Table 11: Liletta Trial L102: Yearly Pearl Index for mITT Population*

	N=1538	On-Treatment Pregnancies	Number of Cycles	Pearl Index	95% Confidence Interval
Year 1	1276	2	17175	0.15	(0.02, 0.55)
Year 2	1035	4	14205	0.37	(0.10, 0.94)
Year 3	860	1	11760	0.11	(0.00, 0.62)
Year 4	720	1	9891	0.13	(0.00, 0.73)
Year 5	598	1	8335	0.16	(0.00, 0.87)
Year 6	321	0	5091	0.00	(0.00, 0.94)

* Excluding cycles with other BCMs used.
Source: 6Y CSR Section 14.1, Tables 1.1 and 10.3.1. Confirmed by analysis of Biostatistics Reviewer, Weiya Zhang, PhD.

Table 12: Liletta Trial L102: Cumulative Pearl Index for mITT Population*

	N	On-Treatment Pregnancies	Number of Cycles	Pearl Index	95% Confidence Interval
1 Year	1538	2	17175	0.15	(0.02, 0.55)
2 Years	1538	6	31380	0.25	(0.09, 0.54)
3 Years	1538	7	43140	0.21	(0.08, 0.43)
4 Years	1538	8	53031	0.20	(0.08, 0.39)
5 Years	1538	9	61366	0.19	(0.09, 0.36)
6 Years	1538	0	66457	0.18	(0.08, 0.33)

* Excluding cycles with other BCMs used.
Source: 6Y CSR Section 14.1, Table 10.1.1. Confirmed by analysis of Biostatistics Reviewer, Weiya Zhang, PhD.

Table 13 presents the cumulative pregnancy rates in the mITT population using **Life Table** analysis. Cumulative pregnancy rates are similar with or without the exclusion of cycles during which other BCMs were used. This suggests the contraceptive effect is primarily due to the Liletta IUS, because the analysis shows that concurrent use of another BCM does not significantly decrease the pregnancy rate.

Table 13: Liletta Trial L102: Life Table Analysis for mITT Population (N=1545)

	No Cycles Excluded	Cycles With Other BCM Use Excluded
	Cumulative Pregnancy Rate (95% CI)	Cumulative Pregnancy Rate (95% CI)
Year 1	0.14 (0.04, 0.57)	0.14 (0.04, 0.57)
Year 2	0.49 (0.22, 1.09)	0.50 (0.22, 1.10)
Year 3	0.59 (0.28, 1.25)	0.60 (0.29, 1.27)
Year 4	0.72 (0.36, 1.45)	0.73 (0.36, 1.48)
Year 5	0.87 (0.44, 1.70)	0.89 (0.45, 1.75)
Year 6	0.87 (0.44, 1.70)	0.89 (0.45, 1.75)

Source: 6Y CSR Section 14.1, Tables 11.1 and 11.7. Confirmed by analysis of Biostatistics Reviewer, Weiya Zhang, PhD.

In conclusion, efficacy was evaluated and shown by the pregnancy rate based on the Pearl Index calculation that excluded cycles with other-BCMs-used and the Life Table method with no cycles excluded:

- The yearly PIs, including a Year-6 PI = 0.0 (95% CI: 0.00, 0.94), based on 66,457 evaluable cycles.
- The 6-Year cumulative PI = 0.18 (95% CI: 0.08, 0.33), with the upper bound of the 95% CI consistently below or close to 1.
- The 6-year Life Table (cumulative) pregnancy rate = 0.87 (95% CI: 0.44, 1.70).

The primary efficacy results, based on the yearly and cumulative PI point estimates and the supportive cumulative Life Table methods of analysis of pregnancy rates, consistently demonstrate that the Liletta IUS is effective in preventing pregnancy for up to six years of product use. There are no concerns regarding the statistical analyses submitted in this Efficacy Supplement (S008). The Biostatistics review division verified the statistical analyses conducted by the Applicant. Efficacy evaluations by the statistical and clinical reviewers are consistent. Refer to the Biostatistics Review by Weiya Zhang, PhD, September 18, 2019.

Data Quality and Integrity

Data quality and integrity are satisfactory as demonstrated by thorough study assessments and complete narratives. The numbers of subject discontinuations are not excessive upon yearly or cumulative evaluation. The reasons for subject discontinuations are in line with a study population of reproductive age and do not indicate a new trend or raise concern.

Efficacy Results – Secondary and other relevant endpoints

Given that the endpoint (pregnancy occurring during IUS-use) occurs infrequently, the pregnancy rate estimations by subgroups is inconclusive. However, selected parameters are discussed below for presentation purposes. In general, the results by subgroups are consistent with the overall analyses.

The efficacy results by **age** (< 18, 18-30, and 31-35 years) and **race** (White and non-White), excluding cycles with other reported BCM use, are presented in **Table 14** and **Table 15**, respectively. Seven of the nine on-treatment pregnancies occurred in women 18 to 30 years of age and two occurred in women 31-35 years of age at study entry. Eight of the on-treatment pregnancies occurred in white women and one occurred in an African-American woman. The on-treatment pregnancy rates stratified by age and race are acceptable, with overlapping CIs suggesting differences are not due to differences in product effectiveness. The upper bound of the 95% CI is generally in the 1-3 range, except in the Non-White group, but acceptable overall.

Table 14: Liletta Trial L102: Life Table Analysis by Age in mITT Population*

	< 18 Years of Age N=11	18-30 Years of Age N=1230 (95% CI)	31-35 Years of Age N=304 (95% CI)
Year 1	0.00	0.09 (0.01, 0.64)	0.36 (0.05, 2.50)
Year 2	0.00	0.43 (0.16, 1.14)	0.78 (0.19, 3.09)
Year 3	0.00	0.57 (0.23, 1.36)	0.78 (0.19, 3.09)
Year 4	0.00	0.73 (0.32, 1.65)	0.78 (0.19, 3.09)
Year 5	0.00	0.94 (0.44, 2.02)	0.78 (0.19, 3.09)
Year 6	0.00	0.94 (0.44, 2.02)	0.78 (0.19, 3.09)

* Excluding cycles with other BCMs used. For results with no cycles excluded, refer to 6Y CSR Section 14.1, Table 11.2
Source: 6Y CSR Section 14.1, Table 11.8. Confirmed by analysis of Biostatistics Reviewer, Weiya Zhang, PhD.

Table 15: Liletta Trial L102: Life Table Analysis by Race in mITT Population*

	White N=1255 (95% CI)	Non-White N=286 (95% CI)
Year 1	0.18 (0.04, 0.70)	0.00
Year 2	0.60 (0.27, 1.34)	0.00
Year 3	0.73 (0.35, 1.54)	0.00
Year 4	0.73 (0.35, 1.54)	0.79 (0.11, 5.46)
Year 5	0.92 (0.45, 1.89)	0.79 (0.11, 5.46)
Year 6	0.92 (0.45, 1.89)	0.79 (0.11, 5.46)

* Excluding cycles with other BCMs used. For results with no cycles excluded, refer to 6Y CSR Section 14.1, Table 11.5
Source: 6Y CSR Section 14.1, Table 11.11. Confirmed by analysis of Biostatistics Reviewer, Weiya Zhang, PhD.

Subgroup analysis by baseline characteristics of **parity** and **BMI**, excluding cycles with other reported BCM use, are presented **Table 16** and **Table 17**, respectively.

As in the initial Application and Efficacy Supplements (S004 and S007), parous subjects demonstrate a higher on-treatment pregnancy rate than nulliparous subjects (61.8% of the mITT population). Five of the nine on-treatment pregnancies occurred in parous women while

four occurred in nulliparous women. This minimal difference likely reflects the proven fertility in parous women, as assessed in the CDTL review of the initial application. Overlapping CIs suggest this difference does not indicate reduced effectiveness in parous women.

Pregnancy rates also differ among BMI subgroups. The on-treatment pregnancy rate is higher in subjects with BMI ≤ 24.9 or BMI ≥ 40 compared to subjects with BMI 25.0-29.9 or BMI 30.0-39.9. Seven of the nine on-treatment pregnancies occurred in the normal weight group, one in the overweight group, and one in the morbidly obese group. Limiting factors confound these findings. The BMI ≥ 40 (morbidly obese) stratum has the highest on-treatment pregnancy rate, 1.71 (95% CI: 0.24, 11.52), but this is driven by a single subject (Subject # (b) (6)) and the limited number of evaluable cycles (reflected in the wide CI around this estimate). The BMI ≤ 24.9 (normal) stratum has a similarly elevated on-treatment pregnancy rate of 1.61. Thus, comparisons across BMI strata do not reveal a trend of decreasing effectiveness with increasing BMI. Limiting factors described preclude conclusions regarding potential differences in effectiveness due to variances in BMI; labeling revisions are recommended, accordingly.

Table 16: Liletta Trial L102: Life Table Analysis by Parity in mITT Population*

	Nulliparous N=954 (95% CI)	Parous N=591 (95% CI)
Year 1	0.00	0.38 (0.10, 1.53)
Year 2	0.27 (0.07, 1.09)	0.88 (0.33, 2.35)
Year 3	0.44 (0.14, 1.36)	0.88 (0.33, 2.35)
Year 4	0.44 (0.14, 1.36)	1.26 (0.51, 3.10)
Year 5	0.69 (0.25, 1.88)	1.26 (0.51, 3.10)
Year 6	0.69 (0.25, 1.88)	1.26 (0.51, 3.10)

* Excluding cycles with other BCMs used. For results with no cycles excluded, refer to 6Y CSR Section 14.1, Table 11.3
Source: 6Y CSR Section 14.1, Table 11.9. Confirmed by analysis of Biostatistics Reviewer, Weiya Zhang, PhD.

Table 17: Liletta Trial L102: Life Table Analysis by BMI in mITT Population*

	BMI ≤24.9 kg/m2 N=795 (95% CI)	BMI 25.0 – 29.9 kg/m2 N=373 (95% CI)	BMI 30.0 – 39.9 kg/m2 N=297	BMI ≥ 40 kg/m2 N=77 (95% CI)
Year 1	0.14 (0.02, 0.97)	0.30 (0.04, 2.10)	0.00	0.00
Year 2	0.64 (0.24, 1.70)	0.30 (0.04, 2.10)	0.00	1.71 (0.24, 11.52)
Year 3	0.85 (0.35, 2.03)	0.30 (0.04, 2.10)	0.00	1.71 (0.24, 11.52)
Year 4	1.09 (0.49, 2.46)	0.30 (0.04, 2.10)	0.00	1.71 (0.24, 11.52)
Year 5	1.41 (0.66, 3.03)	0.30 (0.04, 2.10)	0.00	1.71 (0.24, 11.52)
Year 6	1.41 (0.66, 3.03)	0.30 (0.04, 2.10)	0.00	1.71 (0.24, 11.52)

* Excluding cycles with other BCMs used. For results with no cycles excluded, refer to 6Y CSR Section 14.1, Table 11.4
Source: 6Y CSR Section 14.1, Table 11.10. Confirmed by analysis of Biostatistics Reviewer, Weiya Zhang, PhD.

In conclusion, the preceding efficacy results based on Life Table analyses for various subgroups in the mITT population suggest acceptable contraceptive efficacy for a six-year duration of treatment—regardless of age, race, or parity. However, analyses of data for subgroups (e.g., age < 18 years, BMI ≧ 40 kg/m^2, and other subgroups) is inconclusive: Important trial limitations precluding conclusions about potential differences in effectiveness due to subgroup variances include the low frequency of on-treatment pregnancies with IUS use and the small sample size of several subgroups (with consequently small numbers of evaluable cycles).

Dose/Dose Response

Not Applicable; the Liletta IUS is produced in a single dose.

Durability of Response

Refer to the previous Section on "Efficacy Results - Primary Endpoint" of this review. The on-treatment pregnancy rate is acceptable and stable over time: Year-6 PI of 0.0, Cumulative 6-Year PI of 0.2, and a Life Table Cumulative Rate of 0.92 (95% CI: 0.46, 1.82). Refer to **Table 11**, **Table 12**, and **Table 13**. Although limited conclusions can be made about durability of response across subgroups, it generally appears similar regardless of age, race, parity, or BMI.

Persistence of Effect

The Applicant assessed persistence of product effect by evaluating the time elapsed for return to menses (RTM) and return to fertility (RTF) after Liletta removal in subsets of subjects. Findings suggest no persistent effect after Liletta removal and are acceptable. Refer to the Clinical Pharmacology Review by Peng Zou, PhD, September 10, 2019.

RTM: Overall, 487 of the 499 (97.6%) subjects evaluated for RTM after Liletta discontinuation had a RTM within five months: 97.9% of the Efficacy Group and 92.6% of the older Non-Efficacy Group. Of the 10 subjects in the Efficacy Group who did not have RTM, seven did not because

they became pregnant before having a menses, two had a hysterectomy for reasons unrelated to the IUS, and one had no evaluation for amenorrhea. Of the two subjects in the Non-Efficacy Group, one had a hysterectomy and one had become menopausal. Overall, 470 (94.2%) had a menses within two months following Liletta discontinuation, 483 (96.8%) within three months, and 487 (97.6%) within five months. Excluding the 11 subjects for whom a return of menses would not be expected (i.e., became pregnant first, had a hysterectomy, or became menopausal), 487 of 488 (99.8%) subjects had RTM within five months after Liletta removal. These findings are consistent with those reported in the 120-Day Safety Update.

RTF: Subjects who discontinued Liletta and desired pregnancy were followed for up to 12 months to assess fertility. Overall, 145 (87.9%) of the 165 subjects who were evaluated for RTF reported pregnancy within 12 months of Liletta removal, 96 (78.6%) of which occurred within six months. Three of these subjects were in the older Non-Efficacy Group: two became pregnant, one at five months and the other at 10 months. These findings are consistent with those reported in the 120-Day Safety Update and no labeling changes are indicated.

Additional Analyses Conducted on the Individual Trial

The Applicant conducted secondary analyses on the effect Liletta has on endometrial thickness and the difference in Liletta's pharmacokinetic profile between non-obese and obese subjects.

Endometrial Thickness: The mean endometrial thickness after Liletta placement was 3.8 ± 1.8 mm (n=52, Efficacy Group) using data at baseline and at 12 months, and 3.1 ± 1.5 mm (n=22, Efficacy Group) using data at baseline and at 60 months. These findings are consistent with thinning of the endometrium, a known effect of the progestin drug component in Liletta. This thinning effect would be expected to be the same or more pronounced in the older Non-Efficacy Group.

Pharmacokinetics and Body Mass Index Analysis: The effect of BMI on LNG exposure was assessed in non-obese (BMI ≤ 30 kg/m^2) and obese women (BMI ≥ 30 kg/m^2).

In the PK BMI Substudy [n=41 (Non-obese n=21, Obese n=17), Week 1 through Month 30], the mean plasma LNG concentrations in obese subjects ranged from 25% to 40% lower than in non-obese subjects (60.5% of the concentration of non-obese subjects at week one, 73.1% at Month 12, 64.0% at Month 24, and 67.7% at Month 30). These same Substudy subjects were subsequently followed for months 36, 42, 48, 60 and 72.[4]

In the main L102 trial [n=892 (Non-obese n=673, Obese n=219), Month 36 through Month 72], mean plasma LNG concentrations in obese subjects ranged from 24% to 32% lower than in non-

[4] 6Y CSR Section 11.5.3.1. Pharmacokinetics Studies, pp125-127/257. BMI Substudy subjects comprised of Efficacy Group subjects (16-35 years of age). Main L102 Trial BMI subjects comprised of Efficacy and Non-Efficacy Groups.

obese subjects (72.8% of the concentration of non-obese subjects at Month 36, 72.5% at Month 48, 74.0% at Month 60 and 68.0% at Month 72); this difference was sustained from Year 3 through Year 6 of Liletta use.[5]

In summary, LNG plasma concentrations of obese subjects were observed to be about 25% less than those of non-obese subjects. However, since Liletta has a mainly local progestogenic effect in the uterine cavity, the clinical relevance of systemic exposure is unclear. While comparisons across BMI strata do not reveal a trend of decreasing effectiveness with increasing BMI, trial limitations preclude definitive conclusions about potential differences in effectiveness due to subgroup variances (refer to the discussion in the Section on "Efficacy Results—Secondary and Other Relevant Endpoints" of this review). Accordingly, labeling revisions are recommended to convey these uncertainties.

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

The Applicant is conducting a single open-label Phase 3 pivotal trial (L102) to assess the efficacy, safety, tolerability, and continuation rates of the Liletta IUS. Therefore, an integrated review across multiple trials is not pertinent. Refer to Section 6.1.2. of this review for the assessment on "Efficacy Results" pertaining to primary endpoints and secondary analyses of selected cohorts in Trial L102.

7.1.1. Primary Endpoints

Refer to Section 6.1.1. of this Review.

7.1.2. Secondary and Other Endpoints

Refer to Section 6.1.1. of this Review.

7.1.3. Subpopulations

Refer to Sections 6.1.1. and 6.1.2. of this Review.

[5] *Ibid.*

7.1.4. Dose and Dose-Response

Not Applicable; the Liletta IUS is produced in a single dose.

7.1.5. Onset, Duration, and Durability of Efficacy Effects

Refer to Section 6.1.2. of this Review.

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

The Liletta IUS is already approved for use on the US market and postmarketing data raise no new clinical concerns or signals impacting product benefits.

7.2.2. Other Relevant Benefits

The Mirena IUS, which contains 52mg of LNG like the Liletta IUS, has approval for a secondary indication of treatment of heavy menstrual bleeding (as well as for the primary indication of contraception for up to five years of use). Refer to **Table 2** of this review. Data from the Liletta L102 trial show diminished menstrual bleeding patterns and diminished endometrial thickness with this LNG-containing IUS over time. This suggests Liletta is likely to offer the same benefit for treating heavy menstrual bleeding (HMB) as Mirena. However, a dedicated trial would likely be required if the Applicant decides to add this efficacy claim or pursue an indication for HMB.

7.3. Integrated Assessment of Effectiveness

M360's ES S008 for the ongoing Liletta contraceptive efficacy trial, L102, provides evidence for a level of effectiveness in the prevention of pregnancy through six years of use that meets the statutory evidentiary standard and will offer clinically meaningful benefit. The primary efficacy results, based on the yearly and cumulative PI point estimates and pregnancy rates using the cumulative Life Table methods of analysis, consistently demonstrate that the Liletta IUS is effective in preventing pregnancy for up to six years: a **Year-6 PI = 0.0** (95% CI: 0.00, 0.94) based on 66,457 evaluable cycles, and a cumulative **Six-Year Life Table pregnancy rate of 0.89** (95% CI: 0.45, 1.75). Although the PI increased from Year 1 to Year 2, it subsequently decreased slightly and remains stable through Year 6. (Refer to **Table 1** of this review.) There has been one pregnancy each year from Year 3 through Year 5, and the upper bound of the 95% CI for each year remains <1.0. Despite limitations on analyses, due to the rare occurrence of the primary efficacy endpoint (on-treatment pregnancy) and small subgroup sample sizes, efficacy appears sufficiently similar regardless of age, race, parity, or BMI. The RTM and RTF profiles are acceptable and consistent with IUS products. Refer to Section 6.1.2. "Study Results" for the complete assessment of product effectiveness in Trial L102.

8. Review of Safety

8.1. Safety Review Approach

Refer to **Section 5.2. "Review Strategy"** of this review. The previous reviews of the initial NDA submission (SN0000) and efficacy supplement supporting approval of use with the SHI-001 inserter (SN0031) included safety data through September 1, 2015. The previous review of efficacy supplement S004 (SN0052) to extend duration of product use to 4 years, its respective 120-Day Safety Update, and supplemental data requested by the Division included safety data collected through May 3, 2017. The previous review of efficacy supplement S007 (SN0079) to extend duration of product use to 5 years and its respective 120-Day Safety Update includes data collected through February 26, 2018. This review of efficacy supplement S008 (SN0093) to extend duration of product use to 6 years and its respective 120-Day Safety Update includes data collected through February 28, 2019.

8.2. Review of the Safety Database

Refer to **Section 6.1.1. "Study Design"** of this review for an overview of the trial safety population and respective safety endpoints.

8.2.1. Overall Exposure

The clinical safety database for Liletta in the Phase 3 trial, L102, includes 1751 subjects comprised of generally healthy women 16 to 45 years of age who have provided over (b) (4) 28-day evaluable cycles[6] of exposure. The overall exposure to Liletta by year of use is shown in **Table 18**. A total of 566 women completed six years of product use, through the 120-Day Safety Update period ending February 28, 2019.[7] The Applicant submitted cumulative safety data regardless of years of product use.

[6] Notably, this is the referenced number of cycles of exposure in trial-related narrative in the USPI. However, the number of evaluable cycles of exposure for subjects 16-35 years of age in the mITT population is 66,457.
[7] In comparison, 402 subjects completed six years of use in the August 20, 2018, dataset. Notably, the Applicant provides the number who have reached 7 (n = 194), 8 (n = 150), and 9 (n = 14) years of use.

Table 18: Liletta Trial L102: Liletta IUS Drug Exposure: Yearly through Year-6 of Use

Safety Population[a] Drug Exposure (120-Day Safety Update Through February 28, 2019[b])			
	16-35 Years of Age (N_0=1568)	**36-45 Years of Age (N_0=146)**	**Total Safety Population (N_0=1714)**
Total Women Years[c] [N(%)]			
Year 1	1283 (81.8)	126 (86.3)	1409 (82.2)
Year 2	1049 (66.9)	114 (78.1)	1163 (67.9)
Year 3	866 (55.2)	106 (72.6)	972 (56.7)
Year 4	731 (46.6)	98 (67.1)	829 (48.4)
Year 5	611 (39.0)	91 (62.3)	702 (41.0)
Year 6	486 (31.0)	80 (54.8)	566 (33.0)
Duration of Treatment (Women Months)[d]			
N Subjects	1568	146	1714
Mean (SD)	45.6 (31.2)	63.1 (34.4)	47.1 (31.9)
Median	41.8	78.6	44.9
Min, Max	0.03, 110.1	1.8, 107.1	0.03, 110.1

[a] Only subjects with successful insertions are included.
[b] If the IUS remains in place, the data cut-off date of February 28, 2019, was used for the last date of use.
[c] 1, 2, 3, 4, 5, and 6 years are equivalent to 13 (364 days), 26 (728 days), 39 (1092 days), 52 (1456 days), 65 (1820 days), and 78 (2184 days), 28-day cycles, respectively. A subject is considered to have completed 6 years of use if she has completed the Month 72 Visit.
[d] A woman-month = 30.4 days, where days are calculated as follows: last known date of use — IUS insertion date + 1.
Source: Adapted from 120-Day Safety Update for S008, Table 1, p6/54, (Appendix 2, Table 9.1).

8.2.2. Relevant characteristics of the safety population:

Subject demographics and baseline characteristics are summarized in **Table 8** of this review and proportions appear relatively stable throughout the course of Trial L102.

8.2.3. Adequacy of the safety database:

The Applicant exceeded the requirement of ≥10,000 cycles of exposure in the first year of treatment, ≥200 women who are ≤35 years of age completing the full six-year course of treatment, and ≥20% nulliparae participating in the trial. Refer to **Table 1** and **Table 8** of this review for additional details. A total of 566 women completed six years of product use. The safety database is adequate for review of up to six years duration of product use.

8.3. Adequacy of Applicant's Clinical Safety Assessments

Refer to **Table 5** in **Section 6.1.1. "Study Design"** of this review for an overview of the trial's Schedule of Assessments.

8.3.1. Issues Regarding Data Integrity and Submission Quality

There are no concerns regarding the reported data integrity and quality. The narratives of reported complications are adequate. Overall, the reported complications are consistent with known risks associated with LNG-releasing IUSs.

8.3.2. Categorization of Adverse Events

Refer to Sections 10.4.1 through 10.4.5 this review. The Applicant maps verbatim terms on case report forms to Preferred Terms (PTs) and System-Organ Classes (SOCs) from the Medical Dictionary for Regulatory Activities (MedDRA), version 12.1.

8.3.3. Routine Clinical Tests

Routine clinical evaluations that extend through Year-6 of the trial are comprehensive and include the following tests:

- Vital Signs
- Breast and Pelvic Examinations
- IUS Presence Verification
- Papanicolau Cervical Screening Tests
- Chlamydia/Gonorrhea Tests
- Pregnancy Tests
- Blood Tests—Hemoglobin and Serum Chemistry

8.4. Safety Results

8.4.1. Deaths

One death has occurred in Trial L102 to date, a suicide in a subject with a known history of depression and anxiety occurring approximately one month following IUS insertion (reviewed in the initial NDA submission). The Applicant did not consider this case to be drug-related. However, suicide is potentially associated with LNG-releasing IUS treatment, given the known association between progestins and depression. Accordingly, depression is a labeled adverse reaction based on a rate of 8.3% in Trial L102 (Section 6.1., Table 3 of the USPI) and on findings from trials of LNG IUSs (demonstrating rates of depression/depressive mood between 4.2% to 6.7%). Although the depression rate reported in the Trial L102 is higher than the range reported in the literature, it may reflect different trial conditions (e.g., psychological history of subjects at baseline) rather than a greater risk of depression with use of the Liletta IUS. Nonetheless, the known adverse reaction of depression with LNG-releasing IUSs warrants attention, as described in labeling. The risk of suicide attempts in Trial L102 does not appear to exceed the expected

background rate in the US. There are no additional deaths reported in the trial through February 28, 2019. No changes to labeling are indicated for this safety concern.

The first post-marketing death case report for Liletta was received through the FDA Adverse Event Reporting System (FAERS) on July 25, 2018. The patient died of infection five days following Liletta IUS insertion. Refer to Section 8.9.1. of this review for discussion of this case.

The second post-marketing death case report for Liletta was received through FAERS on July 24, 2019. Further investigation is planned. Refer to Section 8.9.1 of this review for discussion of this case.

8.4.2. Serious Adverse Events

Serious Adverse Event (SAE) data for Trial L102 are reported through August 20, 2018, in S008 and through February 28, 2019, in the respective 120-Day Safety Update; they are summarized as follows.

A total of 82 (4.7%)[8] subjects reported one or more SAEs—comprised of 74 (4.6%) subjects in the Efficacy Group and 8 (5.3%) in the Non-Efficacy Group. This total represents an additional 3 subjects (all in the Efficacy Group) who reported an SAE between the February 26, 2018, and August 20, 2018, datasets. An additional 3 subjects reported SAEs between August 20, 2018 and February 28, 2019. **Table 19** below summarizes the new SAEs in S008 and the respective 120-Day Safety Update. Most SAEs were single-reported in no more than two subjects in any treatment group. The exceptions are nine events of Crohn's disease (eight of which were for one Liletta subject in the Efficacy Group and related to pre-existing Crohn's disease), eight cases of appendicitis, seven cases of ectopic pregnancies, five cases of bipolar disorder, five cases of cholecystitis (two acute), and three cases of cellulitis. Overall, the rate of SAEs is low, and both the frequency and nature are similar to that observed with use of other LNG IUSs.

[8] The rate of SAEs appears to stable at approximately 4%. The initial NDA submission reported a rate of 2.6%; ES S004 reported 4.0% through December 2, 2016; and ES S007 reported 4.2% through February 26, 2018.

Table 19: Liletta Trial L102: Serious Adverse Events

New Serious Adverse Events Not Previously Reported			
Subject ID (Age in Years) Parity Duration of Use	**SAE**	**Narrative**	**Relation to IUS per Applicant**
Serious Adverse Events reported between (b) (6)			
(b) (6) (30) G0P0 Year 5 (70 months)	Cervical Cancer (b) (6)	**Cervical Squamous Cell Carcinoma** (invasive, moderately differentiated). Subject found to have excoriated cervix upon presentation for elective IUS removal. Subsequent evaluation was consistent with a known history of cervical malignancy. Notably, the screening PAP test was negative and subject reported no history of abnormal PAP tests. Subject subsequently declined consent and declined 30-day follow-up.	Not Related (IUS Removed)
(b) (6) (31) G0P0 Year 5 (66 months)	Left-Lower-Lobe Pneumonia (b) (6)	**LLL Pneumonia** treated with intravenous triple-antibiotic therapy X1 dose followed by oral antibiotic therapy during hospitalization. (Diagnosed incidentally during follow-up CT for previously reported SAE of rib fractures following motor vehicle accident, Case # (b) (6).) Subject subsequently discharged with plan to continue oral antibiotics and have follow-up X-ray.	Not Related (IUS Continued)
(b) (6) (35) G1P0 Year 5 (71 months)	Multiple Sclerosis (b) (6)	**Multiple Sclerosis** diagnosed (b) (6), through evaluation following new onset of symptoms. Subsequently hospitalized and treated with intravenous SoluMedrol (methylprednisolone) followed by oral prednisone. Discharged with plan to follow-up to initiate Copaxone (glatiramer acetate) therapy.	Not Related (IUS Continued)
Serious Adverse Events reported between (b) (6)			
(b) (6) (52) G5P2 Year 6 (74 months)	Esophageal Achalasia (b) (6)	**Esophageal Achalasia** treated with Botox injection following evaluation during hospitalization for worsening dysphagia and concurrent 70 lb weight loss over the preceding five months. Subject subsequently discharged following counseling about home-use nasogastric tube, prescribing multiple treatment medications, and planning follow-up assessment for Peroral Endoscopic Myotomy. Additionally, planning follow-up for incidental CT finding consistent with sacral Paget's.	Not Related (IUS Continued)
(b) (6) (40) G4P2 Year 6 (75 months)	Appendicitis (b) (6)	**Appendicitis** (appendiceal mucocoele) treated with laparoscopic appendectomy. (Weight = 310.2 lbs at presentation.) Surgical history included cholecystectomy, sleeve gastrectomy, and salpingectomy for ectopic pregnancy.	Not Related (IUS Continued)
(b) (6) (38) G2P2 Year 8 (103 months)	Diverticulitis (b) (6)	**Diverticulitis** treated with intravenous antibiotics during hospitalization followed by oral antibiotic therapy. Subject subsequently discharged with plan for follow-up colonoscopy.	Not Related (IUS Continued)

The **highest incidence** of SAEs across all Liletta treatment groups, by System Organ Class (SOC), were **psychiatric disorders** (16 subjects [0.9%]) and **infections and infestations** (19 subjects [1.1%]); the Applicant does not consider these related to the IUS or IUS placement. There are no new SAE cases in the Psychiatric SOC reported in S008 and the respective 120-Day Safety Update. Overall, the characteristics and frequency of these cases is low and expected. As discussed in previous reviews by Drs. Lisa Soule and Gerald Willett, the following factors are important in assessing SAEs pertaining to psychiatric disorders for this Efficacy Supplement:

- Overall, 20% of subjects in Trial L102 reported an "abnormal" psychiatric history at enrollment or had a pre-existing psychiatric diagnosis.
- Women with serious underlying medical conditions, including psychiatric conditions, may use intrauterine contraception more commonly because it is reliable and long-acting, with minimal systemic hormonal exposure.
- Although it is unlikely that the Liletta LNG IUS contributed significantly to the psychiatric cases occurring in Trial L102 (given the low systemic exposure to LNG), it is possible that it may have contributed to exacerbation of underlying psychiatric symptoms such as depression.

No new **life-threatening events** were reported in the time interval between the 120-Day Safety Update Report for S007 and the 120-Day Safety Update Report for S008 (February 26, 2018, through February 28, 2019). Over the course of Trial L102, 16 **life-threatening events** were previously reported in 14 Efficacy Group subjects (seven nulliparous and seven parous); none were reported in Non-Efficacy Group subjects. Three of the 16 life-threatening events were classified as treatment-related—all were ectopic pregnancies treated surgically: Subjects (b) (6) in Year-1 of use, Subject (b) (6) in Year-2 of use, and Subject (b) (6) in Year-7 of use. [The additional four ectopic pregnancies reported to date (two in Year-2, one in Year-3, and one in Year-4) were not considered life-threatening.] The thirteen of the 16 life-threatening events that were classified as *not* related to treatment are summarized as follows: bipolar disorder, ischemic stroke, two suicide attempts requiring subsequent hospitalization, stage IV melanoma, traumatic liver injury due to a bicycle-motor vehicle accident, bilateral lacerated wrists due to physical assault, anaphylaxis due to bupropion allergy, road traffic accident, and suicide. Additionally, one subject experienced three life-threatening events related to her renal disease.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

Serious Adverse Events Leading to IUS Discontinuation

There is 1 new SAE reported, cervical carcinoma, associated with IUS discontinuation (refer to Table 19, Subject (b) (6) in Year-5 of use). However, M360 does not include this case with the previously reported 11 SAEs that resulted in IUS discontinuation.[9] The rationale for this

[9] Of the 11 previously reported SAEs resulting in IUS discontinuation, 8 were considered related to the IUS (1 ovarian cyst requiring laparoscopic cystectomy and 7 ectopic pregnancies—all occurred in the Efficacy Group) and 3 were considered unrelated to the IUS (Stage IV Melanoma, Ewing's Sarcoma, and Celiac Disease).

exclusion is not provided; however, it may be due to the subject having an underlying disease (cervical carcinoma) that was not identified at screening and would have precluded enrollment. No SAEs resulted in IUS removal between the (b) (6) and (b) (6), datasets.

Cumulative Adverse Events Leading to IUS Discontinuation

Table 20 below summarizes cumulative AEs leading to IUS discontinuation. In the total Safety Population, 19.2% of subjects discontinued IUS use due to an AE—4.0% due to expulsion and 15.4% due to other AEs (refer to Table 6 of this review). There were 11 new discontinuations due to AEs reported between the (b) (6) data accrual dates. Of these 11 discontinuations due to AEs, 4 were due to expulsions (the majority of IUS expulsions occurred during the first year of use—50 of 69 expulsions). The other 7 new discontinuation due to AEs are summarized as follows:

- Subject (b) (6) *Libido Decrease*, severe in severity. Assessed as probably IUS-related per Investigator. Resolved at the end of the subject's participation.
- Subject (b) (6), *Polycystic Ovaries*, moderate in severity. Assessed as not IUS-related per Investigator. Ongoing at the end of the subject's participation.
- Subject (b) (6), *Metrorrhagia*, mild in severity. Assessed as probably IUS-related. Ongoing at the end of the subject's participation.
- Subject (b) (6), *Ectopic Pregnancy*, moderate in severity. Assessed as probably related. Resolved on (b) (6). [Note, the discontinuation narrative became available between the (b) (6), and (b) (6), data accrual dates; however, the AE (ectopic pregnancy) was previously reported.]
- Subject (b) (6), *Migraine*, mild in severity. Assessed as not IUS-related per Investigator. Resolved at the end of the subject's participation.
- Subject (b) (6), *Mood Altered*, moderate in severity. Assessed as probably IUS-related per Investigator. Resolved at the end of the subject's participation.
- Subject (b) (6), *Vaginitis Bacterial (VB)*, mild in severity. Assessed as not IUS-related per Investigator. Resolved at the end of the subject's participation. [Note, this subject discontinued IUS use between the (b) (6), data accrual dates; however, the AE (VB) was previously reported.]

The new AE-related discontinuations do not introduce any clinically significant changes to the overall safety profile for Liletta. As in previous reports, only expulsions (3.8%) and acne (1.4%) account for > 1% of overall Liletta discontinuations. Combining all types of bleeding events (i.e., amenorrhea, dysfunctional uterine bleeding, menorrhagia, menstruation irregular, metrorrhagia, and vaginal hemorrhage) accounts for 2.3% of discontinuations due to AEs.

Table 20: Liletta Trial L102: Discontinuations Due To AEs in >0.5% Of The Safety Population

Adverse Event [a] Reason for Discontinuation (Preferred Term)	# AEs Cumulative as of August 20, 2018			# AEs Cumulative as of February 28, 2019	Change
	16-35 Years of Age N=1600 [n (%)]	36-45 Years of Age N=151 [n (%)]	Total N=1751 [n (%)]	Total N=1751 [n (%)]	
Intra-uterine contraceptive device expelled [b]	62 (3.9)	7 (4.8)	68 (4.0)	69 (3.9)	+1
Acne	24 (1.5)	1 (0.7)	25 (1.4)	25 (1.4)	0
Weight increased	17 (1.1)	1 (0.7)	18 (1.0)	18 (1.0)	0
Mood swings	12(0.8)	2(1.3)	14(0.8)	14 (0.8)	0
Dysmenorrhea	17 (1.1)	1 (0.7)	18 (1.0)	18 (1.0)	0
Menorrhagia	15 (0.9)	1 (0.7)	16 (0.9)	16 (0.9)	0
Metrorrhagia	6 (0.4)	2 (1.3)	8 (0.5)	8 (0.5)	0
Vaginal haemorrhage	3 (0.2)	2 (1.3)	5 (0.3)	5 (0.3)	0
Uterine spasm	12 (0.8)	1 (0.7)	13 (0.7)	13 (0.7)	0
Pelvic pain	10 (0.6)	0	10 (0.6)	10 (0.6)	0
Dyspareunia	9 (0.6)	1 (0.7)	10 (0.6)	10 (0.6)	0

[a]Includes only events with *both* incidence > 0.5% *and* > 1 subject in at least 1 treatment group.
[b]Data from Efficacy Supplement S008 (SN0093): 6Y CSR (August 20, 2018 dataset) Section 10, Table 4, p89/257, and Section 14.1, Table 29, p1-2/11; and 120-Day Safety Update (February 28, 2019 dataset), Table 11, p22/54.
Sources: 6Y CSR Section 12.3.2., Tables 49 and 50, pp170-171/257; and Section 14.1., Tables 1.2, 18.3, and 18.4; Summary of Clinical Safety (August 20, 2018 dataset), Section 2.7.4.2.1.4., Table 14, p 28/78; and 120-Day Safety Update, Table 11, p22/54.

8.4.4. Significant Adverse Events

The uncommon but serious Adverse Events of Special Interest (AESI) known to be associated with LNG-releasing IUSs include ectopic pregnancies, perforation, expulsion, infections/PID/endometritis/sepsis, and ovarian cysts; **Table 21** below shows the cumulative incidence of these AESIs in the Liletta Trial L102.

Table 21: Liletta Trial L102: Adverse Events of Special Interest (AESIs)

AESI Incidence in Liletta Safety Population N = 1751									
Data Cutoff Date (Sequence Number of Source Document for Table 14.1)	**12 July 2013 (0000)**	**30 May 2014 (0007)**	**01 Sept 2015 (0031)**	**09 June 2016 (0052)**	**02 Dec 2016 (0060)**	**01 Sept 2017 (0079)**	**26 Feb 2018 (0084)**	**20 Aug 2018 (0093)**	**28 Feb 2019 (0099)**
AESI	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Ectopic pregnancy	2 (0.1)	4 (0.2)	6 (0.3)	6 (0.3)	6 (0.3)	7 (0.4)	7 (0.4)	7 (0.4)	7 (0.4)
Expulsions	49 (2.8)	59 (3.4)	63 (3.6)	63 (3.6)	64 (3.7)	65 (3.7)	65 (3.7)	68 (3.9)[b]	69 (3.9)[b,c]
Perforations	3 (0.2)	3 (0.2)	3 (0.2)	3 (0.2)	3 (0.2)	3 (0.2)	3 (0.2)	3 (0.2)	3 (0.2)
Ovarian cysts	47 (2.7)	59 (3.4)	70 (4.0)	73 (4.2)	75 (4.3)	78 (4.5)	79 (4.5)	79 (4.5)	80 (4.6)[c]
Uterine infection	10 (0.6)	11 (0.6)	12 (0.7)	12 (0.7)	14 (0.8)	14 (0.8)	14 (0.8)	15 (0.9)	15 (0.9)
PID[a]	7	7	8	8	9	9	9	9	9
Endometritis	3	4	4	4	5	5	5	6	6
Sepsis	0	0	0	0	0	0	0	0	0
Breast cancer	0	0	0	0	0	0	0	0	0

[a] PID = Pelvic Inflammatory Disease
[b] 3.9% if denominator is Safety Population (n = 1751); 4.0% if denominator is the number of subjects with successful insertions (n = 1714).
[c] Subject ID (b) (6) had AE of IUS expulsion on (b) (6), and AE of ovarian cyst on (b) (6) (4 days after discontinuation).
Source: Adapted from 6Y Summary of Clinical Safety S008 (SN0093), Section 2.7.4.2.2, Table 18, pp31-35/78.; and 120-Day Safety Update for S008 (SN0099), Section 2.7.4.2.2.1.a, Table 12, pp23-25/54.

The safety data in Efficacy Supplement S008 are similar to those presented in the original NDA submission and subsequent safety updates. They continue to demonstrate the safety of Liletta throughout the proposed duration of use. Overall, incidences of these AESIs in the Liletta safety population are very low and stabilized at approximately 24-30 months following completion of enrollment. Importantly, they appear consistent with those observed with other LNG-releasing IUSs that are used for an extended duration of time. The Applicant has updated data in the draft labeling to reflect the current dataset, but no changes to the overall safety conclusions are indicated based on current data from the Liletta Trial L102.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

The frequency of key treatment-emergent adverse events (TEAEs) described as safety concerns in labeling are summarized in **Table 22** below. All were previously reported except 1 additional ovarian cyst event (Subject ID (b) (6)) occurring between the (b) (6), datasets. These TEAEs include Adverse Events of Special Interest (AESIs) known to be associated with the use of IUSs and SAEs that are possibly related to the Liletta IUS.

Table 22: Liletta L102 Trial: Key Treatment-Emergent Adverse Events

SAE	Number of Subjects in Safety Population (N = 1751) n (%)
Bipolar Disorder	6 (0.3)
Suicide	1 (0.06)
Suicide Attempt	2 (0.1)
Ectopic Pregnancy[a,b]	7 (0.4)
Ovarian Cyst	4 (0.3)
PID	2 (0.1)
DVT	1 (0.06)
Portal Vein Thrombosis	1 (0.06)

[a] Includes one subject who had both a uterine perforation and an ectopic pregnancy.
[b] One subject had ectopic pregnancy in the 7th year of IUS use (refer to Table 10 of this review).
Source: Adapted from 6Y CSR for S008, Section 12.3.1.2., Table 48 (pp167-170) and narrative, pp89-90/257.

8.4.6. Laboratory Findings

Laboratory findings for the Liletta Trial L102 raise no clinical safety concerns. There are no clinically significant differences in the data reported in this Efficacy Supplement (S008) compared to the data reported in the initial NDA submission, i.e., hemoglobin (6Y CSR Section 12.10), serum chemistry (6Y CSR Section 12.11), urine pregnancy tests (6Y CSR Section 12.12), Pap tests (6Y CSR Section 12.13), chlamydia screening (6Y CSR Section 12.14), or gonorrhea screening (6Y CSR Section 12.15).

8.4.7. Vital Signs

Vital signs data for subjects in the Liletta Trial L102 continue to support a favorable safety profile, showing no clinically significant changes since the initial NDA submission (6Y CSR Sections 12.17 and 12.18).

8.4.8. Electrocardiograms (ECGs)

Not Applicable.

8.4.9. QT

Not Applicable.

8.4.10. Immunogenicity

Not Applicable.

8.5. Analysis of Submission-Specific Safety Issues

Not Applicable.

8.5.1. [Name Safety Issue]

Not Applicable.

8.6. Safety Analyses by Demographic Subgroups

Refer to Table 23 below for a summary safety analyses by demographic subgroups.

Table 23: Liletta Trial L102: Summary of Safety Analyses by Selected Demographic Subgroups

Demographic Parameter	Summary Safety Analyses
Age (Refer to SCS S008, Table 26, pp44-45/78)	• Within the Efficacy Group, AEs were analyzed by age subgroups (16–17 years, 18–30 years, and 31–35 years). In Liletta subjects 16–17 years of age at enrollment, 9 of 11 subjects experienced AEs. The only AEs in this age group that occurred in more than 1 subject were nasopharyngitis (3/11, 27.3%), streptococcal pharyngitis (3/11, 27.3%), bacterial vaginitis (2/11, 18.2%), chlamydial cervicitis (2/11, 18.2%), cervical dysplasia (2/11, 18.2%), papilloma viral infection (2/11, 18.2%), and dysuria (2/11, 18.2%) (6Y CSR Section 12.2.3.1). All pediatric subjects enrolled are now adults. However, inferences regarding AE incidences in this age group are limited by the small number of subjects. (Refer to Table 24 of this review for a comparison of safety-related events between pediatric and adult subjects.) • Overall, the observed frequencies of AEs considered most common (incidence > 5%) across all age subgroups reflect the expected incidence in the general population of sexually active women 18–45 years of age. Differences observed among subgroups within this age range may be a result of differences in the number of subjects enrolled in each subgroup, with smaller numbers of women enrolled in the older age cohorts.
Race (Refer to SCS S008, Table 29, p49/78)	• Overall, there does not appear to be a clinically significant difference in safety profile between Non-White (n=331) and White (n=1416) subjects. Subjects classified as White have AE incidences similar to the total safety population, primarily because they constitute a large proportion (78.4%) of subjects. • Differences between observed frequencies of AEs (e.g., IUS expelled, dysmenorrhea, menorrhagia, and depression) may be a result of differences in the number of subjects enrolled in each subgroup. • Although, the proportion of Whites is slightly higher than that in the general US population, race and ethnicity are not expected to impact the IUS safety profile.

BMI (Refer to SCS S008, Table 28, pp47-48/78)	• Weight increase was reported at a higher rate in women with a higher BMI. Women with a higher BMI had lower systemic levels of levonorgestrel (refer to Section 8.1.2. Study Results, Subsection "Additional Analyses Conducted in the Individual Trial" of this review). Therefore, the observed weight increase may be less attributable to the study product and more likely correlated with other underlying factors associated with obesity. • Inferences regarding AE incidences in morbidly obese women (BMI ≥ 40.0) are limited by the relatively small number (n=93) of subjects enrolled in this cohort. • Other differences in observed frequencies of AE incidences may be due to the smaller number of subjects enrolled in each BMI subgroup (refer to Table 8 of this review), smaller size cohort of Non-White subjects, a higher prevalence of increased BMI in Non-White subjects, or study drug effect. However, analyses by BMI subgroup shows a relatively equal distribution of sample size, thereby possibly lending support to the safety observations pertaining to BMI.
Parity (Refer to SCS S008, Table 27, p46/78)	• Overall, the rates of AEs are comparable between parity groups in the total Safety Population. Analysis of AEs with the most common incidence (> 5%) shows Liletta is generally well-tolerated, with no clinically relevant or unexpected differences between parous (n=740) and nulliparous (n=1011, defined as having no previous deliveries, either vaginal or cesarean, beyond 24 weeks gestation) subjects. • The observed differences (e.g., nasopharyngitis: parous 15% vs nulliparous 28%) may be a function of the number of subjects enrolled in each subgroup, or the relative age disparity between the groups (parous mean age 30.3 ± 6.1 years vs nulliparous mean age of 25.1 ± 4.3 years). • As with other IUSs, the expulsion rate is higher in parous subjects and was reported in the initial NDA submission; no labeling change is indicated based on review of the cumulative data in this submission.

8.7. Specific Safety Studies/Clinical Trials

Following its initial approval for use with a two-handed inserter (THI) device, Liletta was approved for use with a single-handed inserter (SHI-001) on January 29, 2016. Only the SHI has been marketed and distributed since February 17, 2017. Therefore, the Applicant was subsequently released from the post-marketing commitment (PMC) to assess differences in outcomes between the two inserters. Cumulative AEs overall are comparable between the THI and SHI; existing difference appear primarily due to a greater proportion of Mild AEs reported with the SHI.

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

No cases of breast cancer have been reported in Trial L102 through the 120-Day Safety Update accrual date, February 28, 2019. No new concerns related to carcinogenicity of the breast have arisen with LNG or LNG-releasing IUSs that would currently require additional safety evaluation.

Ovarian cysts are identified in Trial L102 only when women complain of symptoms that prompt diagnostic testing; routine ultrasound surveillance is not performed. Refer to Table 21 and Table 22 of this review for additional details. The small increase in incidence is expected due to the increased time on study, and no changes to the labeling are indicated.

Assessment of changes in endometrial thickness in a subset of subjects based on transvaginal ultrasonography at one year, five years, and eight years is one of the secondary objectives of Trial L102.[10] Endometrial thickness was evaluated in fifty-two subjects 16-35 year of age with data at Baseline and Month 12. At Baseline and Month 12, these subjects had a mean endometrial thickness of 4.0 ± 2.4 mm and 3.8 ± 1.8 mm, respectively. Endometrial thickness was evaluated in twenty-two subjects 16-35 year of age with data both at Baseline and Month 60. At Baseline and Month 60, these subjects had a mean endometrial thickness of 3.9 ± 2.3 mm and 3.1 ± 1.5 mm, respectively. These findings are expected and consistent with those in the literature; they support the safety profile of Liletta as it pertains to effects on the endometrium.

[10] This safety sub-study to evaluate the effects of Liletta on endometrial thickness was included in Trial L102 for European Regulatory filing purposes only, because UteronPharma (now Allergan), Medicines360's commercial partner, was pursuing E.U. approval.

8.8.2. Human Reproduction and Pregnancy

Refer to **Table 10** of this review for a summary of all on-treatment pregnancies. There have been 11 on-treatment pregnancies in the Efficacy group to date: nine through year-5 of use, and two in year-7 of use. Two of the 11 on-treatment pregnancies had live-birth outcomes (Subject # (b) (6) in year-1 of use and Subject # (b) (6) in year-7 of use) without reported complications or adverse sequelae for the mother or infant. However, the overall small number of on-treatment pregnancies precludes conclusions regarding product effects on pregnancy. The high proportion of ectopic and failed pregnancies compared to pregnancies with live-birth outcomes is expected and consistent with labeling; therefore, no labeling changes are indicated.

For a discussion on return to menses (RTM) and return to fertility (RTF), refer to Section 6.1.2 Study Results, Subsection "Persistence of Effect", of this review.

8.8.3. Pediatrics and Assessment of Effects on Growth

Effects on growth in the pediatric population are not assessed; the use of this contraceptive product is not indicated in premenarchal girls.

Additional Pediatric Assessments

As noted in Table 23, 11 Liletta subjects were 16–17 years of age at enrollment—all are now adults. No pregnancies occurred in this subgroup. All AEs that occurred in this subgroup were previously reported and are summarized in **Table 24.** The Applicant reports no new findings pertaining to this subgroup or recent literature raising any new concerns about IUS use in adolescents.

Summary of Pre-submission/Submission PREA Activity

The Applicant submitted the iPSP of March 21, 2018, to comply with the pediatric study requirements of the Pediatric Research Equity Act (PREA), which are now invoked with the M360's application for a new indication: contraception for duration of use up to six years.[11] The Applicant based the submitted iPSP on findings from the Liletta Trial L102, which enrolled 11 adolescents (16 through 17 years of age), and the peer-reviewed literature.

On September 6, 2018, the Pediatric Advisory Committee (PAC) approved the Applicant's revised iPSP of March 21, 2018, following concurrence with the Agency's recommendations. The key components of the iPSP are summarized as follows:

- Partial waiver of PREA requirements is granted for boys and premenarchal girls (0-11 years of age);

[11] PREA is invoked each year from six years of proposed product use onward (because there is no precedent product; the Mirena IUS currently has approval only through five years of product use).

- Safety data obtained from adolescent girls 16-17 years of age (in the trial and literature) may be extrapolated to post-menarchal girls 12-15 years of age; and
- A pediatric assessment for post-menarchal adolescent girls 12 to < 17 years of age, based on extrapolation of efficacy data from adults and safety information in adolescents, must be included with each submission requesting approval for each additional year-of-use, for the indication of contraception.

The decision to approve the iPSP was based on the following information:

- There are no physiological reasons a LNG IUS would work differently in adolescents than in adults.
- Data submitted by the Applicant support use in adolescents (refer to Table 24: Liletta Trial L102: Assessment of Use in Pediatric Population Table 24 below):
    - Safety and efficacy findings in adolescents 16 – 17 years of age appears consistent with those in the overall study population.
- Data submitted by the Applicant is consistent with the literature (population-based data).[12, 13]
- A search conducted of FDA Adverse Event Reporting System (FAERS) reports for Liletta (LNG IUS) in pediatric patients through 16 years of age retrieved no U.S. serious pediatric reports, or fatalities, through July 18, 2018. This search was conducted by the Division of Pharmacovigilance (DPV) in accordance with the PREA. DPV did not identify any pediatric safety concerns for Liletta and recommended continuation of routine pharmacovigilance monitoring.

[12] Patseadou M and Michala L. Usage of the Levonorgestrel-releasing Intrauterine System (LNG-IUS) in Adolescence: What is the Evidence So Far. Arch Gynecol Obstet 2017;295:529-541.
[13] Berenson AB et al. Complications and Continuation of Intrauterine Device Use Among Commercially Insured Teenagers. Obstet Gynecol. 2013 May;121(5):951-958.

Table 24: Liletta Trial L102: Assessment of Use in Pediatric Population

Pediatric *vs* Adult Subjects Cumulative Adverse Events of Special Interest (AESI)*						
Age Group	**On-Treatment Pregnancy (Efficacy)**	**AESI (Safety)**				
		Ectopic Pregnancy	**Perforation**	**Expulsion**	**Infection**	**Other**
16-17 Years of Age n=11 9 Subjects Reported AEs. 3 AEs IUS-related.	0	0	1 D#92, IUS Removed (Safety)	0	1 Bacterial Vaginitis D#5	1 Pelvic Pain D#1 1 Mood Swings D#18, IUS Removed (Non-safety)
Adult Women* n=1545	9 On-treatment pregnancy	8	4	69	11 PID 6 Endometritis	96 Ovarian Cysts

* Overall, annual increment in AEs for Year-6 of use is comparable to prior years.
Source: Adapted from Efficacy Supplement S007 UniReview October 15, 2018. Data updated for "Adult Women" per the 6Y CSR for S008.

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Not Applicable.

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

Review of the post-marketing safety data from Periodic Adverse Drug Experience Report (**PADER**) 13 submitted to the NDA since review of the last Efficacy Supplement (S007) finds no new safety concerns; the safety data presented are similar to data in the initial NDA submission and subsequent safety updates.

A query of the FDA Adverse Event Reporting System (**FAERS**) for reports pertaining to IUS ***perforation*** with Liletta use generated the findings shown in Table 25 below, based on the parameters indicated.[14] The overall increases in reported cases over an 18-month period does not raise new concerns. Of note, cases reported as "Device Dislocation" may include expulsions. Additionally, a single report may contain more than one PT, and a single case may be entered in FAERS as a duplicate case with a different report identification number. No new safety concerns were identified.[15]

Table 25: Liletta FAERS Query Summary for Uterine Perforations

Parameter Definition	Parameter		Change
Date of Report Receipt in FAERS From:	February 26, 2015 (Initial Approval Date)	February 26, 2015 (Initial Approval Date)	
Date of Report Receipt in FAERS To:	May 22, 2018	October 14, 2019	18 months
Total Reports:	156	337	+181
Preferred Terms Used:			
Device Dislocation	107	223	+116
Uterine Perforation	51	123	+ 72
Perforation	4	5	+ 1

FAERS received the ***first death*** case report for Liletta on July 25, 2018, for a patient, 33 years of age, who died on (b) (6), following Liletta insertion on (b) (6), and onset of symptoms on (b) (6) (FAERS Case #15196884; Liletta Lot #18009-01). The patient removed the IUS herself on (b) (6). She developed nausea and vomiting the same day which prompted her to go to the Emergency Department; she was subsequently hospitalized, evaluated, and treated with antibiotics prior to her death. The causes of death reported on the death certificate are Toxic Shock Syndrome (TSS) and Sepsis. The Agency conveyed an Information Request (IR) for additional details on July 30, 2018. Some additional information was received, but it did not include confirmatory blood cultures identifying a causative microorganism or the autopsy report. Nonetheless, this case report has sufficient information to conclude that the patient's death is most consistent with toxic shock syndrome, likely secondary to the presence of the Liletta IUS.

FAERS received[16] the ***second death*** case report for Liletta on July 24, 2019, for a patient, 18 years of age, who died on (b) (6), following Liletta insertion on (b) (6), and onset of symptoms on (b) (6) (FAERS Case #16628033; Liletta Lot #1900-01). She developed nausea and severe abdominal pain with cramping that prompted a return visit to her physician on (b) (6). She was evaluated with three ultrasonography examinations, but findings were not clearly reported ("no signs of fever, nothing was going on in pelvis, and no infection;

[14] Query conducted by Miriam Chehab, PharmD, BCPPS, Division of Pharmacovigilance II.
[15] For a full review of FAERS Case Reports pertaining to Uterine Perforation with all IUS Products currently available on the US market (Liletta, Mirena, Kyleena, Skyla, and Paraguard), refer to the Pharmacovigilance Review of June 13, 2018, by Miriam Chehab, PharmD, BCPPS, Division of Pharmacovigilance II, FDA DARRTS Reference ID #4277450.
[16] This report was received from the prescribing physician via a sales representative.

intrauterine device in place; no free fluid, unremarkable adnexa bilateral"). She was treated as an outpatient with ibuprofen and ondansetron. On (b) (6), she was hospitalized until her death the next day. An autopsy was performed, but the report has not been obtained. The proximity of death to the time of IUS placement and presenting symptoms suggests the patient's death is attributable to the presence of the Liletta IUS. However, the reported information is inadequate (e.g., the physician does not provide a rationale or articulate the evidence for assessing the patient had "no signs of fever" or infection). Further investigation is required to make evaluate this case report. An IR from the Agency will be forwarded to the Applicant.

Although extremely rare, ***sepsis*** is a known adverse event associated with IUS use that is documented in the literature and conveyed in labeling for IUS products. The current Liletta labeling section on *Highlights* (under the heading of Warnings and Precautions) notes the risk of (a) "septicemia" and "shock" if pregnancy occurs with Liletta in place, and (b) "Group A streptococcal infection". Other sections of current labeling refer to the risk of "sepsis" more explicitly: Section 5 *Warnings and Precautions*, Section 6 *Adverse Reactions*, Section 8 *Use In Specific Populations* (as a risk pertaining to women who become pregnant with the IUS in place), and Section 17 *Patient Counseling Information*. The Section on *Warnings and Precautions* (Sub-section 5.3) discusses this risk as follows:

> *Severe infection or sepsis, including Group A streptococcal sepsis (GAS), have been reported following insertion of[17] LNG-releasing IUSs. In some cases, severe pain occurred within hours of insertion followed by sepsis within days. Because death from GAS is more likely if treatment is delayed, it is important to be aware of these rare but serious infections. Aseptic technique during insertion of LILETTA is essential in order to minimize serious infections such as GAS.*

For improved clarity and emphasis, the relevant wording in the *Highlights* section of labeling should be the same as the first sentence in Sub-section 5.3.

The Division recommends additional modifications to the Liletta labeling as summarized in Section 10.1. of this review.

8.9.2. Expectations on Safety in the Postmarket Setting

As noted in Section 8.9.1. above, serious and potentially fatal infections secondary to IUS use is a known (albeit rare) risk that is described in labeling. The Division's review team will continue to monitor the risks associated with use of Liletta. If changes in the safety profile of Liletta are identified, additional changes in labeling will be made accordingly.

[17] The term "other" is omitted in the labeling under revision with this Efficacy Supplement (S008) to reflect the reported death cases associated with Liletta use.

8.9.3. Additional Safety Issues From Other Disciplines

There are no additional safety concerns identified by other disciplines; for the complete discussion of safety concerns, refer to Section 8.4 of this review.

8.10. Integrated Assessment of Safety

The clinical safety database for Liletta in the Phase 3 trial, L102, includes 1751 subjects who have provided over (b) (4) 28-day evaluable cycles of exposure. The Applicant provides more than the number of cycles requested by the Division, all in US subjects. Notably, the Applicant enrolled a significant proportion of nulliparous and overweight/obese women. A total of 566 women completed six years of product use, through the 120-Day Safety Update period for Efficacy Supplement S008, for the February 28, 2019, dataset[18]—compared to 402 in the August 20, 2018, dataset.

All AEs in the February 28, 2019, cumulative dataset were expected for the study population, sample size, and duration of the trial. No new safety signals or trends have arisen. The safety data from this dataset are similar to the data presented in the initial NDA submission and subsequent safety updates and continue to demonstrate a safe product profile for Liletta throughout the proposed duration of use for up to six years. The overall safety profile and safety findings are summarized below:

- One death occurred in Trial L102 to date, a suicide in a subject with a known history of depression and anxiety occurring approximately one month following IUS insertion (reviewed in the initial NDA submission). Suicide is potentially associated with LNG-releasing IUS treatment, given the known association between progestins and depression. However, overall, the risk of suicide attempts does not appear to be outside the expected background rate.

- SAEs occurred in approximately 4.6% of subjects[19] participating in Trial L102; this incidence rate appears stable and consistent with the literature. The most common, although still rare, SAEs potentially associated with LNG-releasing IUS use are exacerbation of psychiatric conditions, infections such as PID, ovarian cysts, perforations and expulsions, and ectopic pregnancies. (Seven reported pregnancies were ectopic, all previously reported, for an overall frequency of 0.2% of subjects.) Respective incidence rates appear stable and consistent with rates comparable to other LNG-releasing IUSs.

[18] Number of subjects who completed 7 years is n = 194, 8 years is n = 150, and 9 years is n = 14.
[19] Subjects reporting one or more SAE: n=83. This total represents an additional 6 subjects (all in the Efficacy Group) reporting an SAE between the February 26, 2018, and February 28, 2019, datasets.

- AEs were characterized as follows:
    - Most Common AEs Associated with Early Discontinuation: the most common was device expulsion (4.0%)[20]; others (≥1%) included acne, weight increased, dysmenorrhea, and bleeding complaints, and mood swings[21].
    - Most Common AEs (>5%): included vaginal infections, human papilloma virus test positive[22], acne, nausea, dyspareunia, pelvic pain, breast pain, weight gain, and mood disorders.

- The Applicant conducted secondary analyses that included evaluation of AEs by age, race (White/Non-White), BMI, and parity. Overall, these analyses reveal no clinically significant differences in the incidence of individual AEs by subject subgroups, although small subgroup sizes preclude conclusions regarding differences. A notable exception is the difference in IUS expulsion rates; they occurred more frequently in parous subjects (6.0%) than in nulliparous subjects (2.1%).[23]

- The proportions of subjects who experienced return-to-menses and return-to-fertility, as well as the temporal profiles for these variables, are favorable and similar to those reported in the initial NDA submission, subsequent safety updates, and the literature. The results continue to show a rapid RTM [96.4% within 3 months of Liletta discontinuation, or 99% (567/573) adjusted for 15 subjects who would not be expected to have an RTM due to pregnancy, hysterectomy, or menopause] and RTF [> 50% with pregnancy attained within 4 months of discontinuation, and 83.2% with pregnancy attained within 12 months of discontinuation].

In conclusion, the overall safety profile of the Liletta IUS is acceptable and supports approval for prevention of pregnancy for up to six years of use.

9. Advisory Committee Meeting and Other External Consultations

An Advisory Committee meeting is not required for this efficacy supplement application, that has the sole objective of extending the duration of use of a currently-marketed product, because no questions are raised that require input from external experts.

[20] Discontinuation after expulsion was required per protocol.
[21] The only additional AE reported as associated with discontinuation and occurring at a rate ≥1% between the February 26, 2018, and February 28, 2019, datasets.
[22] The only additional AE reported as occurring at a rate >5% between the August 20, 2018, and February 28, 2019, datasets—likely reflecting increased subject time-in-study.
[23] The difference in IUS expulsion rates between parous and nulliparous women is known, although the underlying cause is not well-understood, but may pertain to differences in the integrity of the cervical os and myometrium.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

The Applicant included revised proposed labeling in the Efficacy Supplement S008 submission of December 26, 2018. In consultation with the Associate Director of Labeling for DBRUP, the Office of Prescription Drug Promotion (OPDP), the Division of Medical Policy Programs (DMPP), and other review disciplines, recommendations and revisions were made pertaining to the Prescriber Information (PI) and the Patient Product Information (PPI) documents. The recommendations and revisions focused on compliance with key regulatory requirements for labeling, preliminary alignment of content and format with the Physician Labeling Rule (PLR), and removing content suggestive of claims regarding product use in adolescents and obese patients (because the small sample size of these subgroups in the trial preclude supporting statistical analyses).

10.2. Nonprescription Drug Labeling

Not Applicable.

11. Risk Evaluation and Mitigation Strategies (REMS)

No risk evaluation mitigation strategies or postmarketing risk management activities beyond the standard labeling and postmarketing safety monitoring were required for the original application. No safety issues or signals were identified that would require initiation of a REMS for this review cycle. The risks associated with LNG-releasing IUSs can be adequately managed in the postmarket setting through product labeling, including the PI and PPI.

12. Postmarketing Requirements and Commitments

The Applicant had a Postmarket Study Commitment (PSC, #2874-1) from February 13, 2015, to characterize the frequency of specific outcomes for the THI-002 inserter and compare it to the SHI-001. However, the Agency released M360 from this PSC on September 13, 2017, because the study was no longer feasible—the THI-002 inserter was no longer marketed or distributed and had been replaced by the SHI. No other postmarketing requirements or commitments were required for approval of the original, or this supplemental, drug application.

13. Appendices

13.1. References

Additional References in S008 (SN0093):

ACOG (2018): Committee opinion no. 735: adolescents and long-acting reversible contraception: implants and intrauterine devices. In Obstet. Gynecol. 131 (5), e130-e139.

Allergan and Medicines360 (2018): Liletta® (levonorgestrel-releasing intrauterine system) Prescribing Information (Reference ID: 4334682).

Bayer HealthCare (2018a): Kyleena (levonorgestrel-releasing intrauterine system). Whippany, NJ, 2018 (Reference ID 4228507).

Bayer HealthCare (2018b): Skyla (levonorgestrel-releasing intrauterine system). Whippany, NJ, 2018 (Reference ID 4064226).

Bahamondes, M.V., Monteiro, I., Canteiro, R., Fernandes, A.S., and Bahamondes, L. (2011). Length of the endometrial cavity and intrauterine contraceptive device expulsion. Int. J Gynaecol. Obstet. 113, 50-53.

Shiri, Rahman; Karppinen, Jaro; Leino-Arjas, Päivi; Solovieva, Svetlana; Viikari-Juntura, Eira (2010): The association between obesity and low back pain. A meta-analysis. In Am J Epidemiol 171 (2), pp. 135–154. DOI: 10.1093/aje/kwp356.

Ventolini, Gary; Khandelwal, Nuvneet; Hutton, Kathryn; Lugo, Jonathan; Gygax, Scott E.; Schlabritz-Loutsevitch, Natalia (2017): Obesity and recurrent vulvovaginal bacterial infections in women of reproductive age. In Postgraduate medical journal 93 (1099), p. 297. DOI: 10.1136/postgradmedj-2016-134638.

13.2. Financial Disclosure

The Certification of Financial Interests and Arrangements of Clinical Investigators (DHHS Form FDA 3454) is completed, signed, and submitted with this Efficacy Supplement. Refer to Section 6.1.2. “Study Results” of this review.

Covered Clinical Study (Name and/or Number): Liletta Trial L102

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 665		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): None		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): None		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) None		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

CAREN KIESWETTER
10/21/2019 03:48:34 PM

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