CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206229Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	February 25, 2015
From	Lisa M. Soule, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	206-229
Applicant	Medicines360
Date of Submission	April 29, 2014
PDUFA Goal Date	February 28, 2015
Proprietary Name / Established (USAN) names	Liletta Levonorgestrel (LNG)-releasing intrauterine system (IUS)
Dosage forms / Strength	IUS containing 52 mg of LNG, inserted into the uterine cavity, to be removed/replaced after three years
Proposed Indication(s)	Prevention of pregnancy for up to 3 years
Recommended:	***Approval***

1. Introduction

There are currently three intrauterine devices or systems (IUS) approved in the US –Mirena (NDA 21-225), which contains 52 mg LNG, Skyla (NDA 203-159) with 13.5 mg LNG, and ParaGard (NDA 18-680, which is non-hormonal, but contains copper, which contributes to the contraceptive effect. Mirena is approved for five years' use for contraception, and has a secondary indication of treatment of heavy menstrual bleeding. Skyla is approved for three years' use for contraception, and ParaGard is approved for ten years' use for contraception.

This application seeks approval for LNG-containing IUS (hereafter referred to as Liletta) that also contains 52 mg of LNG, [redacted] (b) (4) the Applicant currently seeks an indication for only three years' duration of use. [redacted] (b) (4) Compared to Mirena, Liletta has the same drug load; Liletta has an initial daily *in vitro* release rate of 18.6 µg LNG, which decreases to 16.3 µg/day at one year, 14.3 µg/day at two years and 12.6 µg/day at three years after insertion. This level is above the terminal release for Skyla at three years.

[redacted] (b) (4) Skyla is specifically indicated for use by nulliparous women. The ParaGard label makes no mention of parity, although the requirement that the uterus sound to 6-9 cm might exclude some nulliparous patients. The Mirena label states in the Indications and Use section that "Mirena is recommended for women who have had at least one child." Insertion instructions also recommend that the uterus sound to a depth of 6-10 cm.

Professional associations such as the American College of Obstetricians and Gynecologists have encouraged use of IUSs and other long-acting reversible contraceptive (LARC) methods as first-line contraception options in sexually active teenagers[1], without reference to

[1] American College of Obstetricians and Gynecologists, Committee Opinion #539, Adolescents and Long-Acting Reversible Contraception: Implants and Intrauterine Devices, October 2012

parity. The CDC's Medical Eligibility Criteria for Contraceptive Use[2] categorizes the LNG IUS (Mirena) as category 2 (benefits typically outweigh risks) for women younger than 20 years of age, with a comment that concern exists about the risk of expulsion in nulliparae.

One of the Applicant's stated goals is to provide a low-cost option for LARC. Currently approved LNG IUSs cost well over $500; although this cost is amortized over a relatively long duration of use, the out-of-pocket cost may provide a barrier to access for some women. The Applicant states that it will offer Liletta to the US public sector for (b) (4)

2. Background

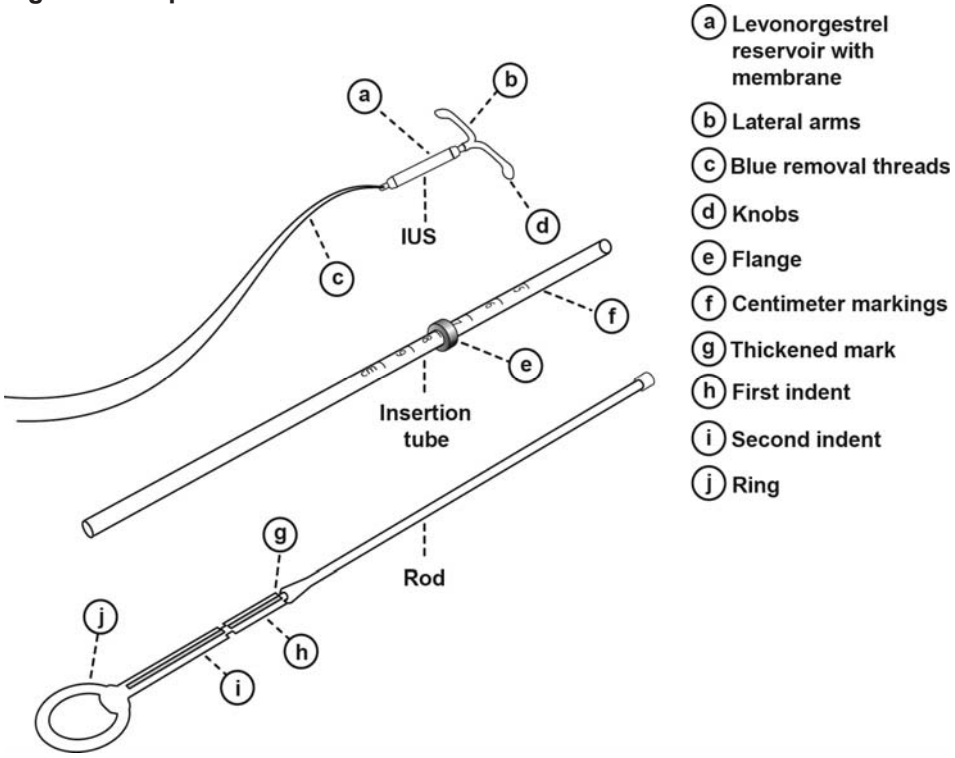
2.1 DESCRIPTION OF PRODUCT

Liletta is a drug delivery system that is regulated as a medicinal product with device components forming an integral part of the system. The IUS comprises a hormone-(b) (4) reservoir that is mounted on a polyethylene T-frame and a polypropylene removal thread attached to the frame. The drug reservoir consists of a mixture of (b) (4) LNG in a silicone base, covered with a polydimethylsiloxane membrane. The frame is compounded with barium to make it radiopaque.

The to-be-marketed inserter consists of a tube with a (b) (4) flange and a (b) (4) pusher used to insert the IUS. The IUS is introduced into the uterus via this single-use, preloaded inserter. Two different inserters were used at various times in the phase 3 trials, and the to-be-marketed inserter has been modified subsequent to the phase 3 clinical trial to facilitate the insertion process. The initial inserter was a two-handed model referred to as THI-001, which was used on about 700 subjects in phase 3. Based on feedback from investigators about patient discomfort and difficult insertions; however, the trial was paused (b) (4) This inserter was then used for the remaining 900 subjects. (b) (4) the Applicant has opted to market Liletta with a modified two-handed inserter, THI-002. As noted in Section 2.2, the Division requested the Applicant to conduct a clinical study to characterize the functionality of the THI-002 inserter; this was done in Study L104. The IUS and inserter are shown in Figure 1. Details of the THI-002 inserter are discussed further in the summary of the CDRH review (Section 6.2) and Study L104 is reviewed in Section 7.4.5.

[2] Centers for Disease Control and Prevention, US Medical Eligibility Criteria for Contraceptive Use, MMWR Recomm Rep 2010: 59 (RR-4): 1-86

Figure 1 Graphic of Liletta and Inserter



Source: Proposed labeling for Liletta

LNG is a progestin commonly used in combination hormonal contraceptives (CHCs), and is a 19-nor-testosterone derivative. It is the active pharmaceutical ingredient in the approved IUSs Mirena and Skyla, which have initial daily *in vitro* release rates of 20 and 14 µg LNG, respectively. Liletta's initial daily release rate is 18.6 µg LNG.

The mode of action for progestin IUSs is based on the local progestogenic effects within the uterus and cervix, including an antiproliferative effect on the endometrium and a weak foreign body reaction. The thickening of cervical mucus inhibits sperm passage through the cervix and effects at the uterus and fallopian tubes also inhibit sperm mobility and function, impeding fertilization.

2.2 REGULATORY HISTORY

The Applicant conducted the drug development program for this indication under IND 105,836. The Division and the Applicant held a preIND meeting in September 2009 to discuss development of a LNG IUS. At this time, the Division agreed that no new nonclinical studies would be required, and confirmed that a 505(b)(2) approach relying on published literature and FDA findings of safety for the Mirena NDA would be sufficient to support nonclinical safety. The Division discussed a planned pharmacokinetics (PK) substudy to be done in the phase 3 trial, and requested additional sampling times, up to the maximum duration of use to be sought. The Division also requested that the Sponsor assess the potential effect of body weight on LNG PK. The Applicant noted that the phase 3 trial would include a small arm of Mirena users, to satisfy European regulatory requirements for a safety comparison. The Division noted that the acceptability of the Applicant's IUS's Pearl Index would be determined on its own merits, not in comparison to that of Mirena, either as

demonstrated in the trial, or based on historical labeled rates for Mirena. Claims of superiority to Mirena would not be allowed. (b) (4) The Division concurred. The Division agreed with the planned enrollment of subjects 16 years and older and of nulliparous women, (b) (4) a sufficient number (i.e., 20% or about 300 women) should be enrolled to support safety and efficacy conclusions in this sub-population. Inclusion of at least 150 women over age 35 was also requested, although these subjects would be excluded from the efficacy population. The Applicant proposed that the study would be powered to determine that the difference between the Pearl Index point estimate and upper bound of the 95% confidence interval (CI) would be < 1. The Division noted that data on a minimum of 200 women completing each year of use should be obtained. The Applicant expressed concern about long-term compliance with a daily bleeding diary. The Division requested that daily diary recording be done for the first two years of the trial; less frequent reporting could be provided as the trial progressed, although the Division was interested in the prevalence of bleeding as the LNG release rate decreases in the final months of use. The Division also requested that use of back-up contraception be recorded in the diary, at least monthly. Cycles in which back-up contraception was used should be excluded from the Pearl Index calculations.

The IND was opened with a protocol for the phase 3 US trial in October 2009. The Division provided comments on the protocol, including:

- Regular sexual activity should be required for entry
- Stratify the safety and efficacy analyses by age, parity and BMI as secondary analyses
- In addition to the Pearl Index, provide a cumulative pregnancy rate and 95% CI for each year of use using Kaplan-Meier or life table methods

The Statistical Analysis Plan (SAP) was submitted in August 2010 and reviewed by the FDA statistical reviewer, who noted that FDA's previous comments had been incorporated. The Division also reviewed amendments to the phase 3 protocol; no further comments were conveyed to the Applicant.

The Applicant submitted a protocol in November 2011 for the phase 1 Study L103, to evaluate the safety (b) (4) inserter (SHI-001). Because the Division did not understand why this was proposed, a teleconference was held in January 2012. During this call, the Applicant explained that the inserter used in the phase 3 trial (THI-001) (b) (4) Study L102 would evaluate the SHI-001 in 50 women, at least 30% nulliparous, and would confirm the location of the IUS after insertion using ultrasound. The IUS would then be removed 5-15 minutes after insertion. Following acceptable results of Study L102, the Applicant intended to use the SHI-001 in the remainder of the phase 3 trial participants.

A guidance meeting about CMC, clinical and regulatory issues was held in June 2012. The Applicant proposed changes to the drug product manufacturing process for commercial production, and use of a new manufacturing facility. Discussion concerned the information needed in the NDA regarding required tests for (b) (4)

(b) (4)

If this were not possible, the Applicant would need to provide *in vivo* data demonstrating similar performance, efficacy and safety to support a proposed manufacturing site change.

The Applicant proposed that the initial NDA submission (for a (b) (4)-year duration of use) would include a minimum of 10,000 28-day cycles and a minimum of 200 women completing two years of use in the efficacy population of women ≤ 35 years at enrollment. About 50% of the population is nulliparous. This was acceptable to the Division. The Division noted that the determination of "on-treatment" pregnancies included those conceived within seven days after IUS removal, based on the margin of error for ultrasound dating. The Division will make its own determination of what it considers to be "on-treatment" pregnancies.

The Applicant noted that more than half the subjects in the phase 3 trial would have used the SHI-001 inserter, and proposed to analyze the efficacy and IUS-related safety data for the study population as a whole, since the inserter would not be expected to impact these parameters. Insertion-related outcomes, such as failure, difficulty, need for cervical dilation and insertion-related bleeding and cramping, would be stratified by inserter. The Division agreed. The Division also agreed that safety data from Study L103 would not be integrated with that from Study L102. In addition, data from a European menorrhagia trial of the LNG IUS conducted by a separate business entity with whom the Applicant has partnered, would be provided as a study report, but safety data would not be integrated with that for the Applicant's contraception trial.

The Applicant requested Fast Track designation and priority review, citing the unmet need for an affordable IUS. The Division indicated that the application did not meet criteria for Fast Track; while priority review status is determined after NDA submission, it did not appear that the application would be eligible for priority review either. The public health benefit based on cost of a product is not a factor FDA can consider.

The revised SAP was submitted in September 2012, and the Division requested that cycles in which a back-up contraceptive method was used be excluded from the life table analysis, and that additional subgroup analyses be done based on inserter type used. The Division also disagreed with the Applicant's plan that subject-reported pregnancies that were not followed-up would not be considered on-treatment pregnancies; the Division will evaluate all pregnancies and make its own determination, typically relying upon a "worst case" approach when data are limited. In a further revised SAP submitted in February 2013, the Applicant accepted the Division's recommendations.

The Applicant requested a meeting to discuss its proposed (b) (4) but the Division denied the request in December 2012 because insufficient information was provided in the meeting request. Guidance was provided regarding the development of the (b) (4).

A preNDA meeting was held in September 2013. The Applicant clarified that its NDA would rely upon its own clinical data, nonclinical studies for which it had right of reference, and information from the public domain (published literature), and that it would not reference

approved Mirena labeling. The Division advised that reliance on published literature that describes a listed drug would require the Applicant to identify the listed drug. The Applicant was encouraged to review recently approved PLR labels for other hormonal contraceptive products, as the draft combination oral contraceptive labeling guidance no longer represents the Division's current thinking. The Division concurred that it appeared that the Pediatric Research Equity Act (PREA) would not apply to this NDA; however, if it were later determined to apply, the Applicant could request a partial waiver for girls < 12 years, and to extrapolate data from adults to postmenarcheal females aged 12 to 15. Girls as young as 16 years were enrolled in the phase 3 trial.

The Applicant planned to seek an indication for three-year duration of use (b) (4) . The primary endpoint, based on the original plan, is the Pearl Index in women aged 16-35 years; however, the Division noted that acceptability of the Year 1 and Year 3 Pearl Indices, as well as a three-year cumulative Pearl Index, would also be important considerations.

The Applicant stated that the to-be-marketed inserter (THI-002) was not one of those evaluated in the phase 3 trial. The Division requested safety and efficacy evaluations stratified by inserter used, as well as a pooled analysis. The specific population described in labeling would be a review issue. The primary analysis should rely upon pooled data, provided there were no notable disparities in efficacy observed across the two inserters. Specific safety analyses should include perforations, expulsions, pelvic infections, ectopic pregnancies, and insertion- and removal-related events. Data on fertility after IUS discontinuation should be provided, as available.

The Center for Devices and Radiologic Health (CDRH) reviewers identified information needed in the NDA to support the THI-002 inserter. The Applicant explained the reason for the change to a novel modified inserter, and noted that the MHRA had approved the inserter absent clinical data in a process similar to a 510(k) device approval; however, MHRA did request a post-marketing safety study of the inserter. The Division noted concerns about higher rates of failed first insertions and "difficult" insertions for the THI-001 compared to the SHI-001 inserter, and requested the following information to support marketing of the THI-002 inserter:

- Conduct a one-day insertion study similar to L-103 with sonographic confirmation of IUS placement using the THI-002 inserter in at least 100 women, about 50% of whom should be nullips. Insertion instructions should be similar to anticipated labeling, and standardized feedback from healthcare providers and patients should be provided about the insertion process. Data on insertion failures, local anesthesia, need for cervical dilation, and insertion-related adverse events (AEs) should be collected.
- Present complication rates for the two phase 3 inserters by person-time, rather than percent of subjects, because length of follow-up was shorter for women using the SHI-001 inserter
- Provide a root cause analysis and bench testing to show that any problems identified in the phase 3 inserters have been addressed and are unlikely to occur with the THI-002 inserter

- Provide evidence that the release rate of the IUS is not impacted by use of the modified inserter
- Provide batch release data on drug product administered using the THI-002 inserter
- Address the stability of the THI-002 inserter
- Provide the protocol for the MHRA-requested postmarketing study of the THI-002 inserter

The Applicant submitted the protocol for phase 1 Study L104 in October 2013 and the Division provided comments, recommending that the IUS be retained for at least 24 hours to allow for evaluation of post-insertion events that did not occur immediately (e.g., expulsion, bleeding, pain, infection). The Division also recommended that a second insertion attempt be allowed, as this would reflect typical clinical practice. The Division agreed to accept the final study report at the time of the 120-day Safety Update.

2.3 PRIMARY MEDICAL REVIEWER'S RECOMMENDATION FOR APPROVABILITY

The primary reviewer, Dr. Dan Davis, stated in his review dated February 23, 2015:

> *Based on the data submitted in Medicines360's (the Applicant's) NDA submission, I recommend that NDA 206229 be approved for the indication of prevention of pregnancy for up to 3 years. This recommendation is based on the Applicant having demonstrated an acceptable Pearl Index (PI) and an acceptable safety profile for this product.*

Dr. Davis did not recommend any postmarketing risk evaluation and mitigation strategies. He recommended a postmarketing study of the THI-002 inserter to be done as a post-marketing commitment.

> **Team Leader Comment:**
> **I concur with Dr. Davis' recommendations, including that of a post-approval study of insertion-related events with the THI-002 inserter, to be conducted as a post-marketing commitment. The Applicant has agreed to conduct such a study. This is discussed further in Section 13.4.**

3. CMC/Device

3.1 CMC

Information about the drug substance LNG was cross-referenced to a Drug Master File (DMF), which previously determined to be adequate in March 2014. The drug product is described in Section 2.1, and consists of an LNG-releasing IUS (T-frame with a drug reservoir around the vertical stem). Adequate controls are in place for non-compendial excipients. (b) (4) used to form the drug reservoir and the (b) (4) membrane were cross-referenced to DMFs, which were reviewed and found adequate. The average daily LNG release over the three-year use period is (b) (4).6 µg/day.

Manufacturing controls were found to be adequate. Proposed specifications reviewed by the primary Chemistry Reviewer, Nina Ni, Ph.D., were deemed adequate to assure the identity, strength, purity and quality of the drug product; however, reviews by the Biopharmaceutics (drug release rate), Microbiology (sterility) and CDRH (inserter functionality) reviewers were not complete at the time Dr. Ni finalized her review. Stability data supported the

proposed expiry of 48 months when stored in the outer carton at 20-25° C until used. No in-use stability data were provided; the lack of such data were acceptable due to the stability data for LNG to 48 months, lack of pharmacology/toxicology concern about the lack of such data, and the precedent of other LNG IUSs having been approved without in-use stability data.

An intercenter consult was sent to the Center for Devices and Radiologic Health (CDRH) to evaluate the modified inserter, which was not used in the registration trials; the consult is discussed further in Section 6.2.

Sites involved in manufacturing, testing and packaging were evaluated by the Office of Compliance. Although the overall recommendation was pending at the time of Dr. Ni's review, the Office of Compliance issues an overall Acceptable recommendation on February 2, 2015.

Dr. Ni provided comments on carton/container labeling, which were conveyed to the Applicant.

Dr. Ni made the following recommendations in her review dated December 19, 2014:

> *The applicant has not provided sufficient information to assure the identity, strength, purity, and quality of the drug product.*
>
> *The Office of Compliance has not made an overall "Acceptable" recommendation for the facilities involved in this NDA.*
>
> *Also, issues on label/labeling have not been resolved.*
>
> *Therefore, from the ONDQA perspective, this NDA is not ready for approval in its present form until all the pending issues are satisfactorily resolved.*

Subsequently, the Applicant submitted acceptable labeling, and the Microbiology, Biopharmaceutics and CDRH reviewers made "approval" recommendations. The Office of Compliance made an "Acceptable" recommendation on February 2, 2015.

Following resolution of these issues, Dr. Ni provided an addendum to her review dated February 11, 2015, in which she concluded:

> *All previous unresolved issues have been satisfactorily resolved. Therefore, from the ONDQA perspective, this NDA is recommended for approval.*

No post-marketing commitments or risk management steps were recommended.

3.2 BIOPHARMACEUTICS

The Applicant made minor changes in the manufacturing process between the phase 3 and to-be-marketed version of the IUS, and provided comparative *in vitro* drug release profiles. The ONDQA Biopharmaceutics reviewer, Kelly Kitchens, Ph.D., reviewed the acceptability of the Applicant's *in vitro* drug release rate method development, the acceptability of the drug release data for the proposed dissolution specification, and the *in vivo* release rate analysis. Dr. Kitchens found that the *in vitro* drug release method, the approach for establishing drug release acceptance criteria and the proposed drug release acceptance criteria were acceptable. The *in vivo* release rate analysis was also found acceptable, and findings will be described in labeling.

Team Leader Comment:
The Applicant did not submit any information relating to an [redacted](b) (4)**.**

Dr. Kitchens made the following recommendation in her review dated January 16, 2015:

> *From the Biopharmaceutics perspective, NDA 206229 for Liletta (levonorgestrel-releasing intrauterine system) is recommended for approval.*

4. Nonclinical Pharmacology/Toxicology

No new nonclinical studies of LNG were requested by the Division, nor were any conducted or submitted by the Applicant. All desired studies to establish the safety of LNG or the materials used in the manufacture of the inserter and drug reservoir have been supported either by published literature or to studies for which the Sponsor has right of reference.

The primary Toxicology Reviewer, Krishan Raheja, Ph.D., made the following recommendations in his review dated December 10, 2014:

> *Recommendations on approvability: Pharmacology/Toxicology recommends approval of the NDA 206229*

Dr. Raheja amended his recommendation regarding nonclinical studies on February 11, 2015 to:

> *Recommendations for nonclinical studies: This section should state that no post-marketing studies are requested or planned.*

Dr. Raheja provided specific labeling recommendations that were conveyed to the Applicant, [redacted](b) (4)

5. Clinical Pharmacology/Biopharmaceutics

The Applicant did not conduct any dedicated studies pertaining to clinical pharmacology, but systemic exposure was evaluated in a PK substudy done as part of the phase 3 trial. Forty subjects had PK sampling at Day 7 and Months 1, 6, 12, 18, 24 and 30 months after insertion, and 243 subjects had sampling done upon completion of 36 months of use. Plasma concentrations of LNG declined from 252 pg/ml initially to 135 pg/ml at Month 36. The Applicant also evaluated the impact of body mass index (BMI) and race on LNG systemic exposure. There was no apparently impact of race; plasma concentrations of LNG were 25-40% lower in obese subjects. The apparent lack of impact of BMI on contraceptive efficacy is further discussed in Section 7.4.3.

No drug-drug interaction studies were conducted, but any effect of enzyme induction or inhibition on systemic LNG levels is not considered to be a critical factor in safety or efficacy because the contraceptive effect of IUSs is mediated through local actions of LNG and a foreign body reaction in the uterus. The systemic levels of LNG are much lower than those associated with use of combination oral contraceptives. Similarly, no studies in renally or hepatically impaired women were conducted, but there is not expected to be an impact of these intrinsic factors on efficacy or safety.

The composition of the phase 3 and to-be-marketed versions of the IUS is the same.

The primary Clinical Pharmacology Reviewer, Li Li, Ph.D., stated the following in her review dated January 30, 2015:

> *The Office of Clinical Pharmacology/Division of Clinical Pharmacology 3 (OCP/DCP3) has reviewed the Clinical Pharmacology sections of NDA 206229. The submission is acceptable from a Clinical Pharmacology point of view pending agreement of labeling recommendations in the package insert.*

Following submission of acceptable labeling, Dr. Li submitted an amendment to her review dated February 24, 2013, in which she concluded that:

> *The Division of Clinical Pharmacology-3, Office of Clinical Pharmacology finds the NDA 203159 acceptable.*

No phase 4 commitments or requirements were recommended.

6. Consultative Reviews

6.1 CLINICAL MICROBIOLOGY

A clinical microbiology consult was requested for this product, and the (b) (4) was reviewed. The reviewer, Denise Miller, made the following recommendation in her review dated January 23, 2015:

> ***Recommendation on Approvability****: Recommended for approval from a quality microbiology perspective.*

No phase 4 commitments were recommended.

6.2 CENTER FOR DEVICES AND RADIOLOGIC HEALTH

The Center for Devices and Radiologic Health (CDRH) Obstetric and Gynecologic Devices Branch was consulted to evaluate the functionality of the to-be-marketed inserter, human factors considerations and other aspects of the device. Several consults were sent to CDRH on the following topics:

- Functionality of the inserter – reviewed by Veronica Price, Biomedical Engineer
- Human Factors – reviewed by Quynh Nguyen, Biomedical Engineer
- Information pertaining to magnetic resonance (MR) labeling, recommended by CDRH for all "implanted devices" –reviewed by Terry Woods, Ph.D.
- CDRH Office of Compliance inspection – a consult was requested to evaluate the medical device constituents of the combination product (IUS + inserter) and determine if an inspection of the manufacturing facilities would be required. Inspection of the manufacturing site, Odyssea Pharma S.A., was recommended, and this was conducted on August 18-22, 2014.

<u>Functionality of the Inserter</u>

Dr. Price reviewed the design, shelf-life, design verification/validation testing and clinical testing of the THI-002 inserter. The initial review revealed certain deficiencies relating to shelf life and design verification/validation testing, and the Applicant was asked to provide additional information. Upon review of the Applicant's response concerning these deficiencies, Dr. Price them to be sufficient. The Applicant provided a design Failure Mode and Effect Analysis (dFMEA) for the inserter and a user FMEA that also evaluated the

inserter. Dr. Price concluded that all identified risks have been adequately controlled through design verification, training and labeling.

Based on investigator feedback part-way through the phase 3 trial, the original THI-001 inserter was discontinued so that the following flaws could be addressed:

(b) (4)

Some of the design changes were also suggested by the MHRA (b) (4) similar LNG IUS that used the same inserter. An additional goal of the redesign was to (b) (4)

Following the trial, (b) (4) related to the SHI inserter, the Applicant developed a modified THI-002 inserter, which is the to-be-marketed inserter. This has the following features to address previous concerns:

(b) (4)

The THI-001 and THI-002 inserter characteristics are compared in Table 1.

Table 1 Comparison of THI Inserters

	THI-001	THI-002
Tube	(b) (4)	
Inserter Tube Tip Incision Length (mm)		1 ± 0.2
Inserter Tube Length (mm)		197.0 ± 1
Inserter Tube OD (mm)		(b) (4)
Inserter Tube ID (mm)		
Plunger (rod, pusher, stem)		
Plunger length without ring (mm)		207 ± 0.8
Plunger Diameter (mm)		2.70 ± 0.10
Plunger tip length (mm)		3.6 ± 0.14
Flange		
Flange inside dimensions (mm)		4.78 ± 0.10
Flange outside dimensions (mm)		11.80 x 7.80
Flange Height (mm)		(b) (4)

Source: Review by Dr. Veronica Price, dated January 23, 2015

Dr. Price reviewed Study L104 and the Applicant's responses to her information request. Regarding the clinical study, she concluded:

> *I agree with the firm that there are a number of confounding factors that make a direct comparison across inserters difficult. The high rates of first attempt success and successful placement provide clinical validation of the effectiveness of the inserter as a delivery system for the LNG20.*

She provided the following conclusion in her review dated January 23, 2015:

> *All of the deficiencies identified in my original review have been resolved. I have no outstanding issues on the THI-002 inserter.*

Human Factors

Dr. Nguyen reviewed the Applicant's user FMEA and its rationale for not conducting human factors validation testing. She made the following conclusion in her review dated October 15, 2014:

> *The Sponsor has submitted a use Failure Modes and Effect Analysis (uFMEA) along with a rationale for why they do not believe a human factors validation testing is necessary on 9/10/2014 in responding to FDA Information Request email. The uFMEA identified some potential patient effects associated with the use of the device that are concerning the human factors reviewer such as hemorrhage, perforation, infection, etc. However, the Sponsor reported that a clinical study report (M360-L104) was submitted as SN0007 to the NDA as 120-day safety update. The Sponsor rationalized that this study confirmed the results of the uFMEA whereby no new risks or unacceptable risk levels were identified, and it also provided evidence that the medical device, as designed, can be used safely and effectively under the actual use conditions in accordance with the instructions for use.* ***Because the actual clinical study supersedes CDRH HFPMET's simulated human factors study requirement, and CDRH HFPMET does not have the expertise to review the clinical study report, this human factors reviewer defers to the medical officer on the team to determine the acceptability of the clinical study results. If it is believed that the clinical study results support the Sponsor's conclusion in terms of no new/unacceptable risks were identified and the device can be used safely and effectively under actual use conditions, then this reviewer will accept the Sponsor's rationale for why a human factors validation study is not needed.***
>
> **Team Leader Comment**
>
> **The clinical review of Study L104 and conclusions regarding its adequacy are discussed in Section 7.4.5.**

MR Testing and Labeling

The Applicant confirmed that Liletta contains no metal determined to be "MRI-conditional." Terry Woods, Ph.D., reviewed the submitted information about MR safety testing and labeling. An extended abstract submitted by the Applicant about MR safety of IUSs generally did not contain sufficient information to determine the MR safety of any of the IUSs evaluated, nor did it demonstrate that the cited testing was applicable to Liletta. However, Dr. Woods determined that because Liletta is composed entirely of polymer materials, and contains no metal, it may be labeled as MR Safe without any testing. A minor labeling revision was conveyed to the Applicant.

Inspection

An additional consult request was submitted to the CDRH Office of Compliance to evaluate the medical device constituents of the combination product and determine if an inspection of the manufacturing facilities would be required. The reviewer, Bleta Vuniqi, determined that information provided to demonstrate compliance with applicable provisions of the Medical Device Quality System Regulation (21 CFR 820) was acceptable. The inspection of Odyssea

Pharma S.A. was classified as No Action Indicated (NAI) and a Form 483 was not issued. The inspection was deemed acceptable. FDA inspection histories were reviewed for additional facilities (b) (4)) and it was determined that inspections were not required prior to approval of the NDA. Bleta Vuniqi had the following conclusion in her review dated January 13, 2015:

> *The Office of Compliance at CDRH has completed the evaluation of application NDA 206629.Sufficient information was provided by the sponsor to demonstrate compliance with applicable provisions of the Medical Device Quality System Regulation (21 CFR 820). NDA 206629 application was determined to be acceptable. Additionally, the inspection of Odyssea Pharma S.A. (FEI # 3007966308) has been conducted and is deemed acceptable.*
>
> *The Office of Compliance at CDRH recommends approvability of NDA 206629 application.*

7. Clinical/Statistical - Efficacy

7.1 OVERVIEW OF CLINICAL PROGRAM

The clinical development program for the LCS12 included a single phase 3 safety and efficacy trial (M350-L102) and two open-label phase 1 studies, each intended to evaluate the functionality of an inserter modified from that originally used in the phase 3 trial. In addition, the Applicant provided data from a European study conducted by another Sponsor using the IUS for the indication of menorrhagia; because this trial studied a different population and indication, the data was not considered supportive of the current application, but safety findings were reviewed at a high level (see Section 8.6).

Study L102 was a three-year phase 3 study that initially included a Mirena arm to address European regulatory filing requirements; this arm was discontinued after 159 Mirena subjects had been enrolled. This arm was not intended to support any comparative conclusions regarding the two IUSs. The study was conducted solely in the US, and included the following sub-studies:

- an *ex vivo* sub-study in 74 subjects to determine the residual LNG content of removed IUSs after one day to three years of use, in order to estimate the *in vivo* release rate over the duration of use (discussed in the Biopharmaceutics review)
- a PK-BMI sub-study in 57 subjects (21 non-obese [BMI < 30] and 19 obese [BMI ≥ 30] subjects using Liletta, and 17 non-obese subjects using Mirena; discussed in the Clinical Pharmacology review)
- an endometrial thickness sub-study (discussed in Section 8.4.1)
- a survey sub-study in 46 clinicians to assess usability of the THI-001 inserter and identify potential design improvements (discussed in Section 7.4.5)

Study L103 was requested by the Division when the Applicant indicated plans to revise the inserter used in the phase 3 study; this study was intended to assess safety and successful placement of Liletta using the SHI-001 inserter. The new inserter was used in 50 nulliparous or parous women, who then had the IUS removed about 15 minutes later. Similarly, Study L104 was requested by the Division to support the to-be-marketed THI-002 inserter, which was not studied in the phase 3 trial. Study L104 used the THI-002 to insert Liletta into 100

nulliparous or parous women; the IUS was retained for 24 hours in this study. Both Studies L103 and L104 used ultrasound to verify correct placement of the IUS.

An overview of the studies is provided in Table 2.

Table 2 Clinical Studies for Liletta

Study Number Phase No. of Sites / Country Dates of Study Conduct	Subject Population	Primary Endpoints	Treatments	Enrolled	Design
M360-L102 Phase 3 29 sites, all US Ongoing; completion of 3 year data in July 2013	Women 16 to 45 years of age, nulliparous or parous	Pearl Index	Liletta	1,751	Multicenter, open-label randomized trial (4:1 to Liletta or Mirena; women > 35 years were assigned to Liletta)
			Mirena	159	
			Total	**1,910**	
M360-103 Phase 1 4 sites, all US Jan. 2012 to Feb. 2012	Women 18 to 45 years of age, parous or nulliparous	Inserter functionality and safety	Liletta with **SHI-001** inserter	50	Multicenter, open-label
M 360-104 6 sites, all US Feb. 2014 to March 2014	Women 18 to 45 years of age, parous or nulliparous	Inserter functionality and safety	Liletta with **THI-002** inserter	100	Multicenter, open-label
LEVOSERT-20 Phase 3 21 sites in Serbia, Romania & Macedonia Dec. 2007 to Sept. 2011	Women ≥ 18 years of age with menorrhagia and 2 episodes of bleeding ≥ 80 ml	Mean menstrual blood loss volume	Levosert	142 for 12 months; 35 for 36 months	Multicenter, randomized, parallel group, single-blind
			Mirena	138 for 12 months; 35 for 36 months	

Source: Based on Table 5.2-1, Tabular Listing of Studies, submitted August 27, 2014

7.1.1 Study L102

Study L102 was a prospective, multicenter, randomized, open-label, two-arm trial, and was the sole phase 3 trial in the Applicant's clinical development program. The objective of the trial was to evaluate Liletta in nulliparous and parous women aged 18 to 45 years.

Notable entry criteria included age 16-45 years (those under 18 years needed parental consent in addition to informed consent from the subject), regular menstrual cycles (21 to 35 days), and regular sexual activity in a monogamous relationship for at least six months. Women were excluded if breastfeeding; if four weeks or less postpartum; for a history of ectopic pregnancy without a subsequent intrauterine pregnancy; recent unresolved uterine, cervical or vaginal infection; current pelvic inflammatory disease (PID) or a history of PID

without a subsequent intrauterine pregnancy; HIV positivity for subject or her partner, history of bicornuate uterus or other uterine abnormality that resulted in distortion of the uterus or cervix incompatible with placement. Notably, there were no exclusions based on parity, weight or BMI.

Investigator training to insert the IUS was conducted by a senior medical advisor who supervised insertion practice on a placebo demo unit after the individual investigator had reviewed instructions, watched a demonstration and practiced on the placebo unit. Investigators were selected for having had prior experience placing other IUSs. Training was conducted on both inserters used over the course of the trial.

LCS insertion was performed within seven days after the onset of menses, or at the end of the duration of use of another contraceptive method; however, for women switching from an oral, transdermal or vaginal hormonal method, they were to continue the original method until the end of the ongoing cycle of use (or for seven days after LCS insertion if the original method was used continuously). Subjects were withdrawn after two failed insertion attempts or following complete or partial expulsion of the LCS, or perforation.

Study L102 enrolled 1,910 women, 1,751 (92%) of whom were randomized to Liletta; this study was conducted solely in the US at 29 sites.

7.2 DEMOGRAPHICS

Demographics were similar in the two arms (Liletta and Mirena) of the study. The mean age of Liletta was about 27 years, and the mean BMI was 26.9 kg/m^2, with a range of 16-62 kg/m^2. About 78% of the subjects were Caucasian, with 13% Black, 4% Asian and 4% "other." About 15% were of Hispanic ethnicity. About 57% of women in each arm were nulliparous.

Table 3 shows the demographics of the Safety population in Study L102, which is defined as all randomized subjects who underwent the IUS insertion procedure. Demographic data categorized by inserter were also provided for the Modified Intent to Treat (MITT) population, defined as all subjects between the ages of 18-35 years who had a successful IUS insertion and had at least one assessment of pregnancy status post-insertion. Although overall, there were 760 women who used the THI-001 inserter, and 991 who had used the SHI-001 inserter, not all of these were in the MITT population. In total, there were 611 women in the MITT who had used the THI-001 inserter, and 934 who had used the SHI-001. Demographics were generally similar for each inserter group, aside from a slightly lower BMI for the SHI-001 subgroup (26.2 vs. 27.6) and a considerably higher proportion of nulliparae for the SHI-001 subgroup (69% vs. 51%).

Team Leader Comments

- **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; overall, 55% would be classified as overweight (BMI > 25), 30% as obese (BMI > 30) and 5% as morbidly obese (BMI > 40).**
- **The cohorts in whom each inserter was used are generally similar. Because it is expected that insertions in nulliparae may be more difficult, the higher proportion**

in the SHI-001 group may result in some overestimation of the actual difficulty using this insertion, compared to the THI-001 cohort.

Table 3 Study L102 – Demographics and Baseline Characteristics – Safety Population

	Liletta Total (N=1,751)	Mirena (N=159)
Age (years)		
Mean(SD)	27.3 (5.7)	26.1 (4.4)
Median	26	25
Ethnicity		
Hispanic or Latina	258 (14.7)	21 (13.2)
Race [N(%)]		
American Indian or Alaska Native	21 (1.2)	2 (1.3)
Asian	68 (3.9)	5 (3.2)
Black or African American	232 (13.3)	12 (7.6)
Native Hawaiian or Other Pacific Islander	6 (0.3)	0
White	1,370 (78.4)	131 (82.9)
Multiple Races Indicated	50 (2.9)	8 (5.1)
BMI (kg/m^2)		
N	1,747	159
Mean(SD)	26.9 (6.8)	27.2 (6.7)
Median	24.9	25.8
Min, Max	15.8, 61.6	17.3, 54.2
BMI 25-29.9 [N(%)]	427 (24.4)	52 (32.7)
BMI ≥30 [N(%)]	438 (25.1)	39 (24.5)
BMI ≥40 [N(%)]	93 (5.3)	11 (6.9)
Partner Status [N(%)]		
Lives with Partner	1,021 (58.3)	84 (52.8)
Does Not Live With Partner	730 (41.7)	75 (47.2)
Nulliparous [N(%)]	1,011 (57.7)	90 (56.6)
Age (years)		
Mean(SD)	25.1 (4.3)	25 (3.9)
Median	25	24
Parous [N(%)]	740 (42.3)	69 (43.4)
Age (years)		
Mean(SD)	30.3 (6.1)	27.6 (4.6)
Median	30	28

Source: Based on Study Report for L102, Table 8, page 98

7.3 DISPOSITION OF SUBJECTS

A total of 2,074 women were screened for the study, with 1,910 enrolled, including 159 who were randomized to receive Mirena. In the Liletta arm, 1,751 women had at least one attempted IUS insertion (151 were > 35 years of age and therefore were not included in the pregnancy efficacy cohort). This total group constituted the safety population. A total of 37 (32 or 2% in the 16-35 year old cohort and 5 or 3.3% in the > 35 year old cohort) had failed placements. Insertion outcome by inserter type is displayed in Table 4.

Table 4 Insertion Outcome by Inserter Type

Outcome	THI-001 n (%)	SHI-001 n (%)	Total n (%)
Initial attempt	760	991	1,751
Successful insertion	689 (90.9)	954 (96.3)	1,643 (93.9)
D/c after failed 1st attempt	23 (3.0)	7 (0.7)	30 (1.7)
Second attempt*	48 (67.6)	30 (81.1)	78 (72.2)
Successful insertion	42 (87.5)	29 (96.7)	71 (91.0)
D/c after failed 2nd attempt	6 (12.5)	1 (3..3)	7 (9.0)
Overall success rate	731 (96.2)	983 (99.2)	1,714 (97.9)

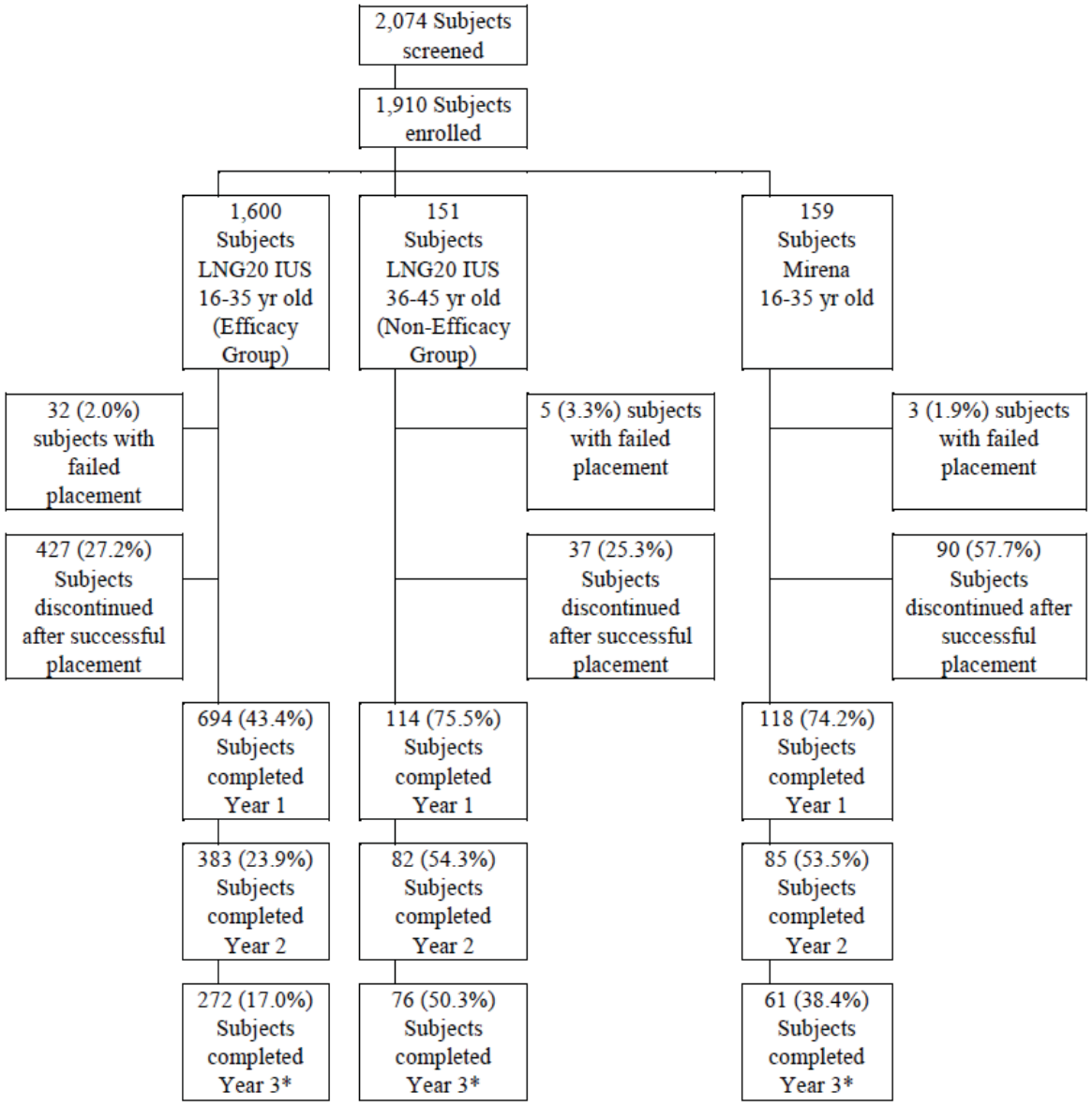
***percent based on proportion of failed first attempt subjects**
Source: Based on Table 56, Study Report for L102, page 163

Team Leader Comments

- **The rate of successful insertion at each attempt was higher with the SHI-001 inserter.**
- **More subjects discontinued after a failed first attempt with the THI-001 inserter, which suggests that the procedure may have been less well-tolerated.**
- **Additional data discussed in Dr. Davis' review showed that the highest frequency of insertions rated "difficult" by the investigators (24%) was in nulliparous women using the THI-001 inserter, and the lowest frequency (4%) was in parous women using the SHI-001 inserter. In both parity categories, insertion using the SHI-001 was more often rated as "easy" or "neutral."**
- **Overall, the success rate after two attempts is acceptable for both inserters.**

The disposition of subjects over the initial three years of the study is displayed in Figure 2. Reasons for premature discontinuation are provided in Table 5.

Figure 2 Subject Disposition, First Three Years*



*Not all active subjects have reached 1 year, 2 years and 3 years of participation.

Note: Each year is inclusive of those subjects having completed the prior year; not all continuing subjects have reached each year of exposure.

***NOTE: Completion numbers do not reflect updated exposure from the Safety Update**
Source: Study Report for L102, Figure 6, page 83

Table 5 Number and Reasons for Premature Discontinuation, MITT Population

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

*** Only applicable for subjects who have a successful placement and discontinued. Percentage based on the total number of treated subjects within each corresponding treatment group.**
Source: Modified from Table 4, Statistical review by Kate Dwyer, Ph.D., dated February 23, 2015

Team Leader Comments

- **Per Figure 2, the completion rate at each year of the study appears to vary markedly across the 16-35 year old and the > 35 year old cohort, as well as between the Liletta and Mirena arms. This is actually an artifact of the phased enrollment. As noted in Section 2.1, after the 760 women who used the THI-001 were enrolled, there was a pause of 20 months before enrollment was restarted for the 991 women who used the SHI-001 inserter. The majority of subjects > 35 years and Mirena subjects had been enrolled in the first phase of enrollment; therefore, their time on study is greater.**
- **The numbers completing each year of treatment in Table 5 have not been updated from the original submission.**
- **The two "Sponsor decision" withdrawals were for a suicide attempt and of a subject working outside the country.**
- **The "investigator decision" withdrawals were primarily due to non-compliance and potential health concerns.**
- **Reasons included in the "other" category were predominantly desire to have IUS removed, but not specified why (53%), and desire to use another method of birth control (25%).**

7.4 EFFICACY FINDINGS

7.4.1 Assessment of Efficacy in Study L102

Routine pregnancy testing was done using high-sensitivity urine pregnancy tests at Screening and at Months 1, 3, 6, 12, 18, 24, 30, 36, and at any premature discontinuation visit. Any positive pregnancy test was to be followed by a serum quantitative hCG and a transvaginal ultrasound to confirm, locate and date the pregnancy. Subjects recorded use of back-up contraception on a daily basis in the subject diary. Days for which no information regarding back-up contraception was recorded were considered days without such use.

Pregnancy was defined as a positive blood or urine pregnancy test; site confirmation of reported pregnancies included urine pregnancy test or quantitative serum hCG at the study site and ultrasound. On-treatment pregnancy was defined as including those conceived during or within 7 days after use of the IUS.

7.4.2 Primary Efficacy Analysis

The primary endpoint was the Pearl Index, calculated as X/E, where X = number of pregnancies, and E = exposure time, expressed as the number of evaluable 28-day cycles of exposure, in accord with the usual calculation used for hormonal contraceptives:

$$\text{Pearl Index} = \frac{100 \times \text{number of pregnancies} \times 13 \text{ cycles/year}}{\text{Number of 28-day cycles of treatment*}}$$

* Only cycles in which no back-up contraceptive methods were used were included.

The final cycle of use (e.g., for subjects still on study when the Pearl Index was calculated) was considered complete if it was ≥ 23 days long, or if a pregnancy was conceived in that cycle.

The analysis population was the MITT population, defined as all subjects between the ages of 18-35 years who had a successful IUS insertion and had at least one assessment of pregnancy status post-insertion. Cycles in which back-up contraception was used were excluded from evaluable cycles, except that the Applicant did not exclude initial cycles post-insertion in which an additional method of contraception was also used, because this was allowed by the protocol.

Evaluable cycles excluded any cycles in which an alternate method of birth control was used. Information on use of back-up contraception was collected in the daily diaries; missing information was imputed as no use of back-up contraception.

Team Leader Comments:

- **The population used by the Applicant is the appropriate one for evaluation of the primary endpoint (Pearl Index). However, the protocol required women to use back-up contraception during the first cycle following insertion, and the Applicant's Pearl Index calculation included these initial cycles as "at-risk" cycles in the denominator. The Division did not agree, and requested the Applicant to recalculate the Pearl Index, excluding these cycles. Results reported hereafter were calculated in accord with the Division's standard.**
- **The efficacy data in the original NDA submission included all pregnancies and cycles of exposure through July 12, 2013. With the 120-day Safety Update and a subsequent 15-day safety report, the Applicant reported four more pregnancies.**

The Division requested that the Applicant recomputed the pregnancy statistics, with an updated denominator to reflect the additional cycles of exposure since the initial submission. The Applicant complied, providing updated data through December 19, 2014. These data are reflected in the tables and discussion in this review.

The Applicant calculated Pearl Indices for Year 1, 2 and 3 individually, and cumulative Two-Year and Three-Year rates.

Life table methods or Kaplan-Meier analyses are also commonly used to assess contraceptive efficacy; these provide cumulative rates of pregnancy at the end of the study, and at the end of each preceding cycle. Life table methods do not typically exclude individual cycles for a given subject, such as a cycle in which an alternate method of birth control was used, but more commonly censor a subject from the remainder of the trial as soon as she uses back-up contraception, or include all of a woman's cycles without regard to use of back-up contraception. For this reason, these analyses are often not directly comparable to the Pearl Index.

The Applicant performed life table analyses that did not exclude cycles in which back-up contraception was used, and a secondary analysis using "absolute time," which excludes cycles in which back-up was used, but then counts subsequent cycles after such use in the total exposure. Life table rates were also calculated for sub-groups based on age, parity, race, BMI and inserter.

7.4.3 Primary Efficacy Results

A total of 43 pregnancies occurred in Liletta subjects in Study L102, and 11 in Mirena subjects. The 43 Liletta pregnancies are classified as follows:

- Two occurred in women > 35 years; both were conceived more than 7 days post-discontinuation of Liletta
- 34 occurred in in the MITT population post-treatment (12-327 days post-IUS discontinuation)
- Six occurred in the MITT population on-treatment, during the first three years of treatment, the duration of use evaluated in this application
- One occurred in the MITT population on-treatment, but in Year 4 and is not included in the pregnancy rate calculations

One Mirena pregnancy was conceived on-treatment (two days post-IUS discontinuation); the others were not considered on-treatment, as they occurred 21-449 days after discontinuation.

Of the six on-treatment pregnancies, all but two occurred in parous women, and four were ectopic; details are shown in Table 6. Two of the pregnancies occurred in the first year, four in Year 2 and none were conceived in Year 3.

Table 6 Details of On-treatment Pregnancies

Study L102				
Subject ID	**Exposure year**	**Parity**	**Inserter Used**	**Outcome**
110-0030	Year 1 (8 months post-insertion)	Parous	THI-001	**Ectopic pregnancy** treated with open salpingectomy during which IUS was not found; on a subsequent laparotomy, **IUS** noted to be **protruding from the posterior uterine wall** near the internal os.
103-2033	Year 1 (9 months post-insertion)	Parous	SHI-001	**Intrauterine pregnancy**, **IUS not visible** on ultrasound. The patient refused further imaging to locate the IUS until after the pregnancy. She delivered a healthy baby at 38 weeks; no further information provided about the IUS.
130-2019	Year 2	Parous	SHI-001	**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. Morbidly obese (BMI 42)
101-2098	Year 2	Parous	SHI-001	**Ectopic pregnancy** treated with laparoscopic salpingectomy. Ultrasound visualized **IUS in the uterus**.
135-2025	Year 2	Nulliparous	SHI-001	Patient presented with pain and elevated hCG (1,065). Ultrasound found complex free fluid in abdomen, no intrauterine pregnancy, no adnexal masses, but identified **IUS in uterus**. Patient taken to OR for suspected **ectopic pregnancy**. The IUS was removed and uterine curettage did not identify chorionic villi or trophoblast. 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 post-op.
133-2091	Year 2	Nulliparous	SHI-001	**Ectopic pregnancy** treated with methotrexate. Ultrasound visualized **IUS in the uterus**; it was removed.
125-0005*	Year 4	Parous	THI-001	**Ectopic** pregnancy initially treated with methotrexate, but underwent laparoscopy two weeks later with sparing of the affected fallopian tube. IUS noted on ultrasound to be abnormally positioned in the cervix, and it was removed in the ER.

*** Pregnancy NOT counted in computing the Pearl Indices for Years 1-3**
Source: Study Report for L102, Pregnancy Listing and Narratives, Section 14 and additional Narratives submitted on February 10, 2015

Team Leader Comments

- **The initial study report included Subjects 110-0030 and 103-2033, as well as Subject 125-0005. Three additional pregnancies were reported in the 120-Day Safety Update, and one further pregnancy was reported in January 2015, as a 15-day safety report.**
  - **Subject 125-005 had an ectopic pregnancy reported; however, this was conceived 3 years, 3 months post-insertion, so it is not counted in the current calculations, which evaluate use of Liletta for up to three years duration.**
- **Of the seven pregnancies, in four cases it was noted that the IUS was located within the uterus. One pregnancy was associated with a perforation and partial expulsion, while the IUS was not visualized for the intrauterine pregnancy that**

went to term. The Year 4 pregnancy ultrasound report suggests that the IUS had been partially expelled (in the cervix). Thus, at most five pregnancies (four in the first three years of use) occurred in the face of normal placement within the uterus.

Pearl Index

The statistical reviewer, Kate Dwyer, Ph.D., reviewed the Applicant's data recalculated to include the three additional pregnancies reported in the Safety Update and January 15, 2015 safety report. The Pearl Index for each year of use and the cumulative three-year Pearl Index are shown in Table 7 for both the MITT and Safety populations. Her calculations confirm those of the Applicant.

Table 7 Pearl Index Calculation

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

Source: Table 4, Statistical review by Kate Dwyer, Ph.D., dated February 23, 2015

Team Leader Comments

- **The Division had requested at least 10,000 cycles of exposure in the first year of use, and 200 women completing three years of use; both of these were met.**
- **The Pearl Indices for each year and the cumulative three-year Pearl Index are acceptable.**

The Applicant also looked at efficacy in subgroups by parity, BMI and race (see Table 8). These calculations are based on the updated pregnancies and cycles through December 19, 2014, and represent cumulative rates over the initial three years of the study.

Table 8 Cumulative Pearl Index by Parity, BMI and Race Subgroups

Subgroup	Evaluable Cycles	# of Pregnancies	Pearl Index	95% CI
Year 1				
Parity				
Nulliparous	10,761	0	0	-, 0.45
Parous	6,364	2	0.41	0.05, 1.48
BMI				
< 25	8,927	1	0.15	0.0, 0.81
25 – 29.9	4,093	1	0.32	0.01, 1.77
30-39.9	3,207	0	0	-, 1.49
≥ 40	867	0	0	-, 5.52
Race				
White	14,060	2	0.18	0.02, 0.67
Non-white	3,015	0	0	-, 1.59
Year 2				
Parity				
Nulliparous	18,837	2	0.14	0.02, 0.5
Parous	10,982	4	0.47	0.13, 1.21
BMI				
< 25	15,463	4	0.34	0.09, 0.86
25 – 29.9	7,195	1	0.18	0.0, 1.01
30-39.9	5,541	0	0	-, 0.87
≥ 40	1,557	1	0.83	0.02, 4.64
Race				
White	24,439	6	0.32	0.12, 0.69
Non-white	5,297	0	0	-, 0.91
Year 3				
Parity				
Nulliparous	21,544	2	0.12	0.01, 0.44
Parous	13,167	4	0.39	0.11, 1.01
BMI				
< 25	17,834	4	0.29	0.08, 0.75
25 – 29.9	8,388	1	0.15	0.0, 0.86
30-39.9	6,534	0	0	-, 0.73
≥ 40	1,867	1	0.7	0.02, 3.87
Race				
White	28,467	6	0.27	0.1, 0.6
Non-white	6,148	0	0	-, 0.78

Source: Communication from the Applicant, dated February 16, 2015

Team Leader Comments

- **The Pearl Index stratified by inserter is not presented, because the inserter type would only be expected to have an impact on insertion success, ease and AEs occurring around the time of the insertion procedure. However, the Applicant looked at this in the original submission and found nearly identical Pearl Indices for the first year of use (THI-001: 0.19 [0, 1.06] and SHI-001: 0.22 [0.01, 1.21]).**

- **Although the > 40 BMI stratum (morbidly obese) has a higher Pearl Index than other BMI strata, this is driven by a single subject (130-2019); the limited number of evaluable cycles are reflected in the wide CIs around this estimate, and limit the conclusions that may be drawn about this. In the lower BMI strata, there does not appear to be any signal of decreased efficacy in higher BMI women.**
- **The higher Pearl Index in parous women may reflect their proven fertility; the overlapping CIs suggest that this difference is evidence of reduced effectiveness in parous women.**
- **Confidence intervals overlapped across strata in each subgroup analysis. With the exception of the morbidly obese subgroup, the upper bound of the 95% CI was < 2 in all subgroups.**
- **The Pearl Indices and CIs for the various subgroups, provides evidence of acceptable contraceptive efficacy for a three-year duration of treatment, without regard to BMI, parity or race.**

Life Table Analysis

The Applicant provided cumulative Life Table estimates of the pregnancy rate over successive years of the study based on the original pregnancy reporting, while the FDA statistician updated the estimates to include the additional pregnancies reported in the Safety Update and the January 2015 safety report (see Table 9). Dr. Dwyer did not exclude cycles in which back-up contraception was used, as this would have resulted in censoring a subject and discounting the remainder of her exposure data subsequent to her first use of back-up contraception.

Table 9 Life Table Estimates of Cumulative Pregnancy Rates

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

Source: Table 5, Statistical review by Kate Dwyer, Ph.D., dated February 23, 2015

Team Leader Comment

The cumulative pregnancy rate is acceptable at each year of use, with the upper bound of the 95% CI consistently below 1.0. Based on Dr. Dwyer's recommendation, the labeled cumulative three-year pregnancy rate should reflect the life table estimate.

Statistician's Conclusion

Dr. Dwyer confirmed the Applicant's overall primary efficacy findings, using the updated pregnancy reports as of January 15, 2015. She did not identify any statistical issues of concern. Dr. Dwyer made the following conclusions and recommendations regarding contraceptive efficacy in her review dated February 23, 2015:

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

7.4.4 Secondary Efficacy Analysis - Bleeding Profile

Characterization of the bleeding profile was considered a safety endpoint. Subjects completed a daily diary that recorded occurrence and intensity of bleeding or spotting for the first 24 months of the study; subsequently, bleeding information was collected by interview during study follow-up visits or contacts (every three months). Women were instructed to indicate whether bleeding was "irregular" or "regular (periods)." The following bleeding intensity categories were used:

- None
- Spotting
- Light
- Moderate
- Heavy

Bleeding was considered a treatment-emergent adverse event (TEAE) if the diary indicated that bleeding was heavier than when not using hormones. Amenorrhea was defined as the absence of bleeding throughout the reference period (90 days) being assessed.

The 28-day bleeding and spotting data are presented in Table 10 and Table 11, respectively. These data reflect all bleeding/spotting, regardless of whether "scheduled" or "unscheduled." Because the IUS insertion frequently occurred during menses, the first month data likely reflects this menstrual bleeding; data from Month 2 on are more reflective of the effect of Liletta on bleeding patterns.

Table 10 Bleeding Days per 28-Day Cycle (First 13 Cycles, then at Year 2)

Cycle	N	Mean (SD)	Min	Median	Max
1	1,691	5.8 (5.2)	0	5.0	28
2	1,650	4.1 (4.8)	0	3.0	28
3	1,620	2.9 (3.9)	0	2.0	28
4	1,525	2.3 (3.3)	0	1.0	28
5	1,444	2.1 (3.1)	0	0	28
6	1,378	1.9 (2.9)	0	0	28
7	1,223	1.5 (2.6)	0	0	23
8	1,039	1.5 (2.7)	0	0	28
9	1,012	1.4 (2.6)	0	0	24
10	997	1.3 (2.3)	0	0	14
11	959	1.2 (2.4)	0	0	16
12	891	1.1 (2.2)	0	0	18
13	791	1.2 (2.3)	0	0	20
26	438	0.8 (1.7)	0	0	10

Source: Study L102 Report, Section 14.1, Table 27.7, pp 1-9

Table 11 Spotting Days per 28-Day Cycle (First 13 Cycles, then at Year 2)

Cycle	N	Mean (SD)	Min	Median	Max
1	1,691	8.9 (6.0)	0	8.0	28
2	1,650	6.8 (6.1)	0	5.0	28
3	1,620	5.2 (5.3)	0	4.0	28
4	1,525	4.3 (4.2)	0	3.0	28
5	1,444	3.5 (3.9)	0	3.0	27
6	1,378	3.3 (3.7)	0	2.0	26
7	1,223	3.0 (3.6)	0	2.0	26
8	1,039	2.8 (3.5)	0	2.0	19
9	1,012	2.6 (3.3)	0	2.0	12
10	997	2.6 (3.3)	0	2.0	21
11	959	2.5 (3.0)	0	2.0	22
12	891	2.5 (3.2)	0	1.0	28
13	791	2.7 (3.4)	0	2.0	28
26	438	2.0 (2.7)	0	1.0	19

Source: Study L102 Report, Section 14.1, Table 27.10, pp 1-9

The rate of amenorrhea increased from 0.6% at the first 90-day period of use, to 19.3% at Year 1, 26.4% at Year 2 and 38.0% at Year 3 (although a diminishing number of subjects were followed at each successive interval.)

Team Leader Comments

- **Subjects consistently had more spotting than bleeding days during each cycle and the number of each decreased steadily throughout the first year of treatment and at Year 2.**
- **The overall bleeding/spotting profile appears acceptable, with about 3-4 days per 28-day cycle by the second six months of use.**
- **The rate of amenorrhea increased over the course of treatment and is similar to that reported (about 20%) at the end of Year 1 for Mirena.**

Return to menses was assessed in women who discontinued the IUS and did not start a hormonal contraceptive. Overall, 99% resumed menses within one year of removal (this excludes three subjects who became pregnant); with 72% resuming by the first month post-removal, and 97% within the first three months.

7.4.5 Data on Inserters

Initial concerns about the THI-001 inserter were noted mid-way through Study L102. After pausing the study, the Applicant surveyed investigators regarding their experience with the THI-001 to identify potential areas for design improvements. Sixty-two investigators with insertion experience using the THI-001 were contacted and 46 (74%) responded. Findings of the survey included:

- More than half preferred a single-handed inserter
- 70% reported the tip of the inserter tube to be too rough and recommended that the taper be more gradual
- 49% reported that the step in which the insertion tube was passed through the cervical os was difficult/very difficult

- 36% reported kinking of the tube during insertion especially where the cervical os was tight, as in nullips
- Other noted concerns included the markings on the inserter and the sliding of the flange
- 98% thought the inserter should be changed

The Applicant decided to redesign the inserter, and developed a one-handed model, the SHI-001. Prior to using it in the remaining subjects to be enrolled into Study L102, the Division requested a small clinical study to verify the functionality of the new inserter.

Study L103 - SHI-001 Inserter

Study L103 was conducted in 50 women (31 nulliparous) who had the Liletta IUS inserted using the SHI-001 inserter. Placement was verified by ultrasound, and then the IUS was removed minutes later. Endpoints included successful insertion, need for cervical anesthesia or dilation, rates of uterine perforation and IUS expulsion, ease of placement and AEs. Only a single insertion attempt was allowed.

Insertion was successful in 48 women (96%), and correct intrauterine placement was confirmed in all. Insertion was unsuccessful in one parous and one nulliparous subject. Overall, 78% had successful placement with no associated AEs (81% in nulliparae, 74% in parous women). There were no expulsions, although the follow-up time after insertion was only minutes. Local anesthesia to the cervix for tenaculum placement was used in the majority (56%) but only 6% of subjects (all nulliparous) required additional anesthesia for discomfort related to sounding or insertion. Cervical dilation was needed in 6% of subjects (2 nullliparous, 1 parous). The insertion was considered "easy" in 98% of cases and "neutral" in 2%. From the subject's perspective, 88% considered the procedure "easy" while 8% considered it "difficult." Cramping or pain was reported by 94%, with nulliparous women more likely to report moderate/severe pain (22% vs. 8% in parous women). Forty-eight women completed a post-insertion questionnaire, and 92% reported they would be willing to have an IUS placed in the future.

From a safety perspective, there were no SAEs or deaths, and no subjects discontinued due to an AE. The only AE that occurred in more than a single subject was metrorrhagia (10%); single subjects experienced AEs including presyncope, application site bleeding, dysmenorrhea and dyspareunia.

Study L104 - THI-002 Inserter

Subsequent to the completion of Study L102, (b) (4) Therefore, it proposed a modified two-handed inserter, the THI-002, for marketing. As noted, the Applicant was requested to conduct a clinical study of insertions using the THI-002 inserter. Study L104 was conducted at six sites in the US, with the objective to assess the proportion of successful placement of Liletta using the THI-002 inserter. Additional assessments were made for safety, need for local anesthesia and cervical dilation, ease of placement, subject acceptance and pain rating, and AEs occurring in the 24 hours post-placement as well as uterine perforations and IUS expulsions. The utility of the Instructions for Use (IFU) was also evaluated by the healthcare providers (HCPs) doing insertions.

The study enrolled 100 women (57 nullips), who underwent insertion, with removal after 24 hours. A follow-up phone call was made one week post-insertion to assess any AEs. The primary endpoint was proportion of subjects with a successful insertion on the first or second attempt.

Overall successful placement was 99%, with 95 women succeeding on the first attempt. A single parous subject discontinued after an unsuccessful first attempt related to cervical canal abnormalities resulting from a previous myomectomy, while the remaining four women all had the IUS successfully inserted on the second attempt. Reasons for these four failed initial attempts were withdrawal of the IUS when the insertion tube was removed.

Local anesthesia was used at the HCP's discretion, and in all cases was administered prophylactically, rather than out of necessity. Overall, it was used in 44% of insertions (53% of nullips, 33% of parous women). Cervical dilation was needed more often in nulliparous subjects (21% vs. 14% for nullips) but typically required only an os finder in most cases, or a 13F Pratt dilator. Ultrasound guidance was used in a single, parous, subject. Use of these adjunctive measures did not differ in an adverse direction from those observed in Study L102 for the THI-001 or from Studies L102 and L103 for the SHI-001.

Investigators assessed insertions as "easy" for 55%, "neutral" for 26% and "difficult" for 19%. Difficult insertions were evenly distributed by parity, but parous women had a higher proportion of "easy" insertions (70% vs. 44%). Despite being rated as "difficult," 14 of the 19 attempts resulted in successful placement, and four of the five unsuccessful placements succeeded on the second attempt.

Subjects' evaluation of pain during the insertion was measured by VAS scores; however, since they did not control for prophylactic use of analgesics or cervical anesthesia, the scores are difficult to interpret. Overall, nulliparae reported higher mean pain scores. Asked whether they would have another Liletta inserted in the future, 88% responded "yes."

The HCPs completed a questionnaire regarding placement difficulty and rated placement as follows:

- 55% easy
- 26% neutral
- 19% difficult

The following descriptions were provided for the 19 "difficult insertions":

- Difficulty getting inserter through the cervix – 13
    - Insertion tube too flexible to pass through cervix – 8
    - Tube kinked – 3
    - Inserter tube too rigid - 1
- IUS remained in inserter tube upon withdrawal of tube from the uterus – 4
- Additional dilation needed due to difficulty with placement – 3
- Multiple attempts to pass through cervix needed due to extreme uterine flexion – 2
- Need for ultrasound guidance -1
- Cervical stenosis, precluding placement - 1

The instructions dealing with release and fundal positioning of the IUS appeared most problematic to HCPs. On a 5-point scale of "strongly agree" to "strongly disagree," the two questions that received negative responses were:

- Information for loading and final positioning easy to understand/follow – 7.1% disagree
- Rod and insertion tube interaction easy to understand/follow – 7.1% disagree

However, this percentage corresponded to a single investigator. All other aspects of the instructions were rated as understandable (agree or strongly agree) by 80-90% of investigators.

No uterine perforations or IUS expulsions were reported in Study L104. All but one of the 99 subjects with successful insertions returned as scheduled and had successful removal of the IUS 24 hours later. The one exception experienced "presyncope" after leaving the clinical after insertion and had her IUS removed in an emergency department. Removal was not attributed to a safety reason. One serious AE of gastroenteritis was not considered drug- or procedure-related. Other reported ARs are known IUS-related ARs such as bleeding (20%), abdominal pain (20%) and cramping (5%). There were no deaths.

Removal ease by the investigator's assessment was accomplished without difficulty by pulling on the strings by 100% of the investigators.

Team Leader Comment

- **Overall, the insertion success rate is higher than that observed for the THI-001 inserter, and similar to that of the SHI-001 inserter in Study L102. The Applicant also notes that the success rate is comparable to that reported for Mirena and Skyla in various publications.**

7.4.6 Overall Assessment of Efficacy

The contraceptive efficacy study conducted by the Applicant provides evidence of an acceptable level of efficacy for Liletta in the prevention of pregnancy. Although the PI increased from Year 1 to Year 2, no pregnancies occurred in Year 3, and the upper bound of the 95% CI for each year remained ≤ 1.1. The overall pregnancy rate (upper bound) over the three-year course of treatment by life table analysis was 0.24 (0.77). Efficacy was similar regardless of parity, BMI or race.

The bleeding profile is acceptable, and indicates that, while most women will maintain monthly menses, the number of days of bleeding and spotting per 28-day cycle decreases with time. About 1/3 of women became amenorrheic by the third year of use.

8. Safety

The safety database is primarily from the phase 3 study. The two phase 1 studies were reviewed for safety (notable safety findings are noted in Section 7.4.5), but in both, the IUS was removed minutes to hours after insertion, so no long-term safety data are available in these studies. The European study of the Levosert IUS for a different indication was reviewed at a high level.

For ease of review the safety data and exposure discussed here for Study L102 includes information reported in the 120-day Safety Update (see Section 8.8), as well as an additional

ectopic pregnancy based on a January 2015 15-day safety report, along with updated exposure information. The study has accrued a total of 34,711 28-day equivalent cycles for Liletta exposure in the PITT population, and 39,108 28-day cycles overall. A breakdown of women-years of exposure by year of use is shown in Table 12; this is somewhat lower than the current total, because it does not include the additional cycles accrued between June 1, 2014 and December 19, 2014.

Table 12 Cumulative Exposure to Liletta, Study L102

	PITT	Women > 35 years	Total
Total Women Years[2] [N (%)]			
Year 1	1286 (82.0)	126 (86.3)	1412 (82.4)
Year 2	495 (31.6)	96 (65.8)	591 (34.5)
Year 3	307 (19.6)	76 (52.1)	383 (22.4)
Year 4	152 (9.7)	54 (37.0)	206 (12.0)
Duration of Treatment (Women Months)[3]			
N	1568	146	1714
Mean(SD)	22.4 (13.6)	33.8 (16.6)	23.4 (14.3)
Median	19.7	41.7	20.3
Min, Max	0.03, 53.1	1.8, 52.9	0.03, 53.1

Source: Table 19, p 32, Summary of Clinical Safety Update, submitted August 27, 2014

The Applicant exceeded the planned 10,000 cycles of exposure in the first year of treatment, at least 200 women ≤ 35 years of age to complete the full three-year course of treatment and the inclusion of at least 20% nulliparae in the study population.

8.1 DEATHS AND SERIOUS ADVERSE EVENTS

Deaths

One death occurred in Study L102, a suicide in Subject 108-2191, a 30 year old woman who received Liletta using the SHI-001 inserter in March 2013. She had a 10-year history of "mild depression" and had been taking antidepressants for the past year. She reported no complaints or mood changes at her Month 1 visit, but committed suicide the next day. Her boyfriend noted she had been experiencing some work-related stress, but had not given any indication of being suicidal. She was reported by her boyfriend to have made a previous suicide attempt 10 years before, although this was not disclosed at screening. The death was not considered by the investigator to be drug-related.

Team Leader Comment:
Depression can be an adverse reaction to treatment with progestins, and is reported in the labeling of other LNG IUSs to have occurred in about 4-6% of subjects in those drugs' clinical trials. The subject in this case reported concomitant use of antidepressants and indicated a history of depression at screening. However, is unclear whether her depression was exacerbated after LCS insertion. I believe it is plausible to consider this a possibly drug-related death.

Serious Adverse Events

Serious adverse event (SAE) data was reported by the Applicant through the closing date of the Safety Update. Information on the additional ectopic pregnancy reported in the January

2015 safety report has been added to the table below. SAEs occurred in 47 women (2.6%) who received Liletta (and 5 [3.1%] who received Mirena) in Study L102. Selected potential serious adverse reactions (i.e., SAEs that might possibly be related to study drug) are shown in Table 13 and other notable SAEs are discussed below.

Table 13 Potential SARs, Study L102, Safety Population

SAE*	Liletta THI-001 inserter N = 760 n (%)	Liletta SHI-001 inserter N =991 n (%)	Liletta Safety Population N = 1,751 n (%)
Bipolar disorder exacerbation	4 (0.53)	2 (0.2)	6 (0.34)
Ectopic pregnancy* **	2 (0.26)	3 (0.3)	5 (0.29)
Suicidal ideation**	2 (0.26)	1 (0.1)	3 (0.17)
Suicide attempt**	2 (0.26)	0	2 (0.11)
Ovarian cysts	1 (0.13)	1 (0.1)	2 (0.11)
PID	2 (0.26)	0	2 (0.11)
DVT	1 (0.13)	0	1 (0.06)
Portal vein thrombosis	0	1 (0.1)	1 (0.06)
Completed suicide	0	1 (0.1)	1 (0.06)
Depression exacerbation	0	1 (0.1)	1 (0.06)
Ischemic stroke	1 (0.13)	0	1 (0.06)
Bilateral wrist lacerations	0	1 (0.1)	1 (0.06)

***Bold = events I consider possible SARs **As discussed below, suicidality events were often reported in association with worsened bipolar disorder or depression, which are listed separately in this table. ***includes one women who had both a uterine perforation that required surgery and an ectopic pregnancy**
Source: Study L102 Study Report, saes-120d.pdf, Table 18, pp 1-31, and Narratives, Section 14; updated August 27, 2014 and February 10, 2015

Team Leader Comment:

- **Overall, the rate of SARs is low and both the frequency and nature of SARs are similar to that observed for other LNG IUSs.**
- **A total of 10 SAEs in the Psychiatric Disorder System Organ Class (SOC) were reported for Liletta (0.6%) and one (0.6%) for Mirena. The Applicant included a variety of Preferred Terms to characterize these events, which result in some splitting. Upon review, there were a number of SAEs related to bipolar disorder, depression, and suicidality. Overall, 20% of the study population reported an "abnormal" psychiatric history at entry, and many of the subjects itemized here had pre-existing diagnoses. Nonetheless, it remains possible that Liletta may have been associated with an exacerbation of their symptoms. Therefore, I believe that exacerbation of depression or bipolar disorder should be listed in Section 6.1 of labeling. In addition, I consider three of the reports to represent suicide attempts (one successful). However, the rate of suicide attempt among women aged 18-35**

years is about 16/10,000 women[3], so the observed frequency in the Liletta population 3/1,751 or 17.1/10,000 women) is within this range.

- **As noted above, Subject 108-2191 committed suicide one month after Liletta insertion.**
- **Subject 105-2055 reported worsened bipolar depression and suicidal ideation about four months after Liletta was placed. However, in this case, she had a sub-therapeutic lithium level and a positive tox screen, which may account for her symptoms.**
- **Subject 111-0009 enrolled with a history of bipolar disorder, depression and panic attacks, and was admitted for "self-harm" and suicidal ideation nine months after Liletta insertion. Her psychiatric medications were changed and the event resolved after five days of hospitalization.**
- **Subject 111-2034 was hospitalized for "worsened bipolar depression" six months after Liletta insertion. She had a past history of depression and anxiety and presented with prolonged depression, which evolved into a manic episode during her admission. She was diagnosed with bipolar depression, stabilized and discharged after six days.**
- **Subject 122-2061 was hospitalized for a worsening mood disorder three months after Liletta insertion. She had been diagnosed with depression and anxiety shortly before her admission and started on antidepressant and anti-anxiety medications. On the day of admission she became agitated and self-violent (banging her head on the wall). She was discharged to outpatient therapy after four days.**
- **Subject 123-0049 was hospitalized for "manic crisis" two years after Liletta insertion. Her past history included anxiety, depression and suicide attempts and she was taking multiple psychiatric medications. She was discharged after six days with gabapentin added to her drug regimen.**
- **Subject 125-0018 was hospitalized for a bipolar crisis and suicidal ideation 21 months after Liletta insertion. She had a past history of bipolar disorder and was on psychiatric medications. Her symptoms of anxiety and depression had been increasing for the past three months and she had been abusing prescription drugs and marijuana daily. She was hospitalized for 18 days, during which her medication regimen was reinstituted and adjusted. She was again hospitalized six weeks later for suicidal ideation and again had a positive tox screen. She was discharged to outpatient therapy four days later.**
- **Subject 127-0071 attempted suicide five months after Liletta insertion. She had a past history of bipolar disorder and multiple suicide attempts. She overdosed on clonazepam after a fight with her boyfriend. She was admitted the next day with depression, but denied current suicidal ideation, although she reported a three-month history of agitation, anhedonia and recurrent passive suicidal ideation. Her psychiatric medications were adjusted and she was discharged three days later. She was discontinued from the study by the Applicant.**
- **Subject 141-0008 was admitted for worsening bipolar disorder three weeks after Liletta insertion. Past history was positive for depression and bipolar disorder. She reported to her therapist that she had been feeling depressed for a few weeks, and had intentionally overdosed with an unreported drug. She was hospitalized with intermittent suicidal ideation and was medicated and discharged after nine days.**

[3] Women's Health USA 2011, http://www.mchb.hrsa.gov/whusa11/hstat/hshi/pages/217mi.html, accessed February 10, 2015

- **Ectopic pregnancy SARs were reported for Subjects 110-0030, 125-005, 101-2098, 133-2091, and 135-2025, all of whom are discussed in** Table 6.
- **There were several cases of venous thromboembolism (VTE); both are at least potentially associated with Liletta.**
    - **A deep vein thrombosis (DVT) was reported in Subject 115-0021 after two years on Liletta. The subject had a history of Crohn's disease, with multiple hospitalizations during the study, and was on multiple GI medications. She was evaluated for pulmonary embolism and this was negative. No apparent risk factors for VTE were reported. Although users of progestin-only contraceptives are considered to be at lower risk for VTE, cases have been reported with LNG IUSs; therefore, I believe this potentially represents a SAR.**
    - **Subject 135-2055 was hospitalized with a portal vein thrombosis three weeks after Liletta was inserted. Work-up in the Emergency Department included a CT scan that demonstrated a splenic vein thrombosis that extended into the proximal portal vein and a splenic mass suspicious for neoplasm. Biopsy of the mass ultimately revealed a splenic hamartoma (a rare benign malformation often found incidentally). The patient reported her sister had Protein C deficiency and the patient herself had a "slightly low" Protein C level (69%); her thrombosis was considered due to an underlying coagulopathy. No association of splenic hamartoma with VTE is reported in the literature. While Protein C levels < 65% are associated with a four-fold increased risk of VTE[4], it is not clear that the patient's level constituted a risk factor.**
- **Two cases of PID were reported as SAEs, but the latency from time of insertion makes it unlikely that these are SARs.**
    - **Subject 115-0041 was admitted with PID 14 months after Liletta insertion. She had a past history of gonorrhea and chlamydia. She was treated with IV antibiotics and discharged on oral antibiotics. Testing for gonorrhea was positive at the time of follow-up exam several weeks later.**
    - **Subject 120-002 was hospitalized for PID10 months after Liletta insertion. She had a past history of chlamydia, but tested negative for gonorrhea and chlamydia at the time of diagnosis. She had failed outpatient oral antibiotics and was admitted for IV antibiotics.**
- **Subject 123-0005 was admitted with an ischemic stroke two months after Liletta insertion; she had been assaulted the previous day, falling to the ground and striking her head. She was noted to have difficulty talking and right-sided facial droop and weakness and was transferred from the Emergency Department to another hospital. Head CT and MRI showed an acute infarct of left middle cerebral artery. An echocardiogram done to rule out a cardiac source of thrombi revealed a patent foramen ovale, but no thrombi. Her physicians believed that the stroke was most likely related to a left carotid dissection not visualized on the MR angiogram. I concur that this is not an SAR.**
- **Subject 141-2071 was hospitalized for bilateral wrist lacerations resulting from an assault with a sharp object by her estranged husband. This does not represent an SAR.**

[4] Fidalgo, T et al. Familial thrombotic risk based on the genetic background of Protein C Deficiency in a Portuguese Study. Eur J Haematol, DOI: 10.1111/ejh.12488; accessed online February 11, 2015

8.2 OTHER ADVERSE EVENTS

8.2.1 AEs leading to Discontinuation

A total of 259 (14.8%) Liletta subjects discontinued prematurely due to an AE. The listing of AEs that caused discontinuation in ≥ 0.2% of subjects in the Liletta arm is presented in Table 14, with related terms bundled as shown. Per protocol, subjects were discontinued if they experienced a partial or complete expulsion. The Applicant's presentation reported discontinuations due to AEs other than expulsion, which was reported separately.

Table 14 AEs leading to Premature Withdrawal in ≥ 0.2% of Subjects

AE leading to withdrawal	Liletta N=1,751	
	n	%
Any Event	259	14.8
Device expulsion	62	3.5
Dysfunctional uterine bleeding, menorrhagia, metrorrhagia or menstruation irregular	4 + 12 + 7 + 3	1.5
Acne	22	1.3
Affect lability, mood swings or mood altered	5 + 14 + 3	1.3
Dysmenorrhea or uterine spasm	11 + 11	1.3
Pelvic pain or pelvic discomfort	9 + 6	0.9
Weight increased	11	0.6
Dyspareunia	8	0.5
Ovarian cyst + polycystic ovaries	6 + 2	0.5
Abdominal or upper or lower abdominal pain	3 + 2 + 1	0.3
Bacterial vaginitis	6	0.3
Headache	6	0.3
Libido decreased or loss of libido	5 + 1	0.3
Depression, depressed mood or emotional distress	1 + 3 + 1	0.3
Abdominal distension	4	0.2
Alopecia or alopecia areata	2 + 1	0.2
Ectopic pregnancy	3	0.2

Source: Based on Summary of Clinical Safety, Table18.3, Appendix 1, updated August 27, 2014

Analyzed by inserter type, 142 women (18.7%) who had the THI-001 inserter discontinued due to an AE, with 31 (4.1%) of these due to expulsion of the IUS. Among women who had the SHI-001 inserter, 117 (11.8%) discontinued due to an AE, with 28 (2.8%) of these due to expulsion.

Team Leader Comments:

- **Overall, the types and frequency of AEs that led to premature discontinuation are consistent with those expected with a LNG IUS.**
- **The apparent higher rate of discontinuations due to AEs overall and to expulsions in the THI-001 arm must be interpreted with caution, because this cohort had more time on study and thus a longer time at risk for discontinuation.**

8.2.2 Common AEs

Overall, by the 120-day Safety Update, AEs had occurred in 1,464 Liletta subjects (83.6%) The most common AEs for Study L102 individually are reported in Table 15, based on AEs

that occurred in at least 5% of subjects. AEs that are clearly unrelated to Liletta (such as respiratory infections) are not included here; however, the list is not limited to those the investigators determined to be drug-related. Therefore, this table represents likely common adverse reactions (ARs).

Table 15 Selected Common Adverse Events (≥ 5%)

Preferred Term	Liletta N= 1,751	
	n	%
Vaginal infection, vaginitis bacterial	13 + 225	13.6
Vulvovaginal mycotic infection or vulvovaginal candidiasis	196 + 37	13.3
Acne or acne cystic	208 + 7	12.3
Headache, cluster headache, migraine, migraine w/ or w/o aura, or tension headache	123 + 1 + 39 + 2 + 1 + 6	9.8
Nausea or vomiting	99 + 39	7.9
Dyspareunia	125	7.1
Abdominal discomfort, pain or upper or lower abdominal pain, or abdominal tenderness	13 + 50 + 34 + 21 + 1	6.8
Breast discomfort, pain, tenderness or nipple pain	1 + 16 + 90 + 11	6.7
Pelvic discomfort, pain	23 + 83	6.1
Adjustment disorder w/depressed mood, affective disorder, depressed mood, depression, emotional distress, or major depression	1 + 2 + 6 + 71 + 9 + 5	5.4
Affect lability, mood altered or mood swings	12 + 40 + 39	5.2

Source: Based on Summary of Clinical Safety Update, Table 14.1, Appendix 1, updated August 27, 2014

AEs occurred at almost identical rates in the two parity subgroups (84.0% in nullips and 83.1% in parous women). There appeared to be little difference in the rate of AEs by insertion type (THI-001: 44%; SHI-001: 56%).

Team Leader Comments:

- **The Applicant reported common AEs by individual preferred terms; I evaluated the overall AE listing and "bundled" related terms, which tends to pick up less common variants that would not otherwise reach the Applicant's threshold for reporting.**
- **Several AEs frequently reported in association with LNG IUSs failed to meet the 5% threshold reported here, including anxiety/agitation (4.9%), vaginal discharge (4.5%), weight increased/weight gain (4.4%), ovarian cysts (4.2%) and bleeding complaints (4.1%).**
- **Many of the AEs are common complaints in reproductive-aged women, and in the absence of a placebo control, it is difficult to determine if they are drug-related. However, a number of them are known progestin-associated AEs (acne, breast symptoms, mood changes, nausea, headache, etc.). Ovarian cysts and bleeding AEs are like to be related to the IUS.**
- **Overall, the rate and types of AEs are not unusual.**

8.3 SUBMISSION-SPECIFIC SAFETY ISSUES

8.3.1 Ectopic pregnancies

There were five ectopic pregnancies in the Liletta arm (0.2%), including two reported in the Safety Update, and one more reported in a 15-day safety report dated January 15, 2015. One

occurred in Year 1, three in Year 2 and one in Year 4. Two ectopic pregnancies occurred in nulliparous subjects and three in parous women. No ectopics occurred in the Mirena arm.

Based on the updated pregnancies and exposure through December 19, 2014, the Applicant calculated the overall ectopic pregnancy rate in the Safety population as 0.12 per 100 women-years. The ectopic pregnancy rate by year and parity is displayed in Table 16.

Table 16 Ectopic Pregnancy Rates by Year and Parity

	Nulliparous Women N = 1,011 n (%)	Parous Women N = 740 n (%)
Year 1	0	1 (0.14)
Year 2	2 (0.2)	1 (0.14
Year 3	0	0
Total*	2 (0.2)	3 (0.41)

*Includes one in Year 4
Source: Updated Summary of Clinical Safety, p 35, submitted August 27, 2014 and communication from Applicant dated February 10, 2015

Team Leader Comments:

- **The risk of ectopic pregnancy with IUSs has been well-characterized; while IUSs prevent both intrauterine and ectopic pregnancy, the proportion of pregnancies that are ectopic is likely to be higher among women using an IUS. However, as above, the absolute risk of ectopic pregnancy is quite low.**
- **Neither of the nulliparous women who had an ectopic pregnancy had to have a Fallopian tube removed; two of the parous women had salpingectomies.**

8.3.2 Pelvic inflammatory disease (PID) and endometritis

In Study L102, there were seven cases of PID and three of endometritis, for an overall frequency of 0.6%. No additional cases occurred after the initial submission. PID occurred in five subjects who had the THI-001 inserter used and two with the SHI-001. Five affected subjects were parous and two nulliparous. Cases of PID occurred within a week of insertion in two cases; the remainder had onset six to 13 months post-insertion. Two cases were considered SAEs, were treated successfully and did not require IUS removal. I agree with the Applicant that these do not appear to be Liletta-related.

Two parous women and one nullip were diagnosed with endometritis. The THI-001 inserter was used in all cases. Endometritis cases started on the day of insertion in two women and on Day 39 in the third. All were considered likely related to IUS placement. Only one resulted in IUS removal; all were treated with antibiotics and recovered.

Team Leader Comment:
PID/endometritis is a known risk of IUDs; the risk associated with Liletta does not appear excessive, but will be described in labeling.

8.3.3 Perforation/embedment

Three perforations occurred in Liletta subjects (no additional cases were reported in the Safety Update). One occurred during sounding, prior to IUS placement (she subsequently had a successful insertion 25 days later). The other two occurred in parous women who had the THI-001 inserter used. One case was noted on the Month 3 visit when her strings could not be seen and ultrasound did not detect the IUS in the uterus. X-ray showed the IUS in the abdomen and it was removed laparoscopically. The second case was identified subsequent to an ectopic pregnancy after about nine months of use; the perforation through the lower

uterine segment into the abdomen was identified in a second surgery following her laparotomy for the ectopic.

8.3.4 Expulsion

Per protocol, subjects were discontinued from the study after partial or total expulsion.

A total of 62 expulsions (3.5%) for Liletta were reported; 35 were partial and 27 complete expulsions. Of the total, the frequency was 2% in nulliparous women and 5.6% in parous women, while expulsions occurred in 4.1% of women who used the THI-001 inserter and 3.1% of those who used the SHI-001 inserter. By time, 50 (81%) occurred in Year 1, 6 (10%) in Year 2 and 2 (3%) in Year 3; the remainder occurred in Year 4.

Table 17 shows the frequency of expulsion by parity, inserter and study year.

Table 17 Total and Partial Expulsions

	THI-001 N=760		SHI-001 N=991	
	Nullips N=348 n (%)	Parous N=412 n (%)	Nullips N=663 n (%)	Parous N=328 n (%)
Year 1	3 (0.9)	19 (4.6)	14 (2.1)	14 (4.3)
Year 2	1 (0.3)	2 (0.5)	2 (0.3)	1 (0.3)
Year 3	0	2 (0.5)	0	0
Total	4 (1.1)	27* (6.6)	16 (2.4)	15 (4.6)

***includes 4 (1 complete, 3 partial) in Year 4.**
Source: Based on Summary of Clinical Safety, Table 22, p 36 from August 27, 2014 update and communication from the Applicant, dated February 23, 2015

The Applicant evaluated expulsions by parity, race, age and BMI. The expulsion rate was higher in parous women (5.5% vs. 1.8% in nullips), non-white women (2.8% vs. 6.0%), rates were similar across age strata. The rate of expulsion increased with BMI category: < 25: 1.7%, 25 to 29.9: 3.5%, 30 to 39.9: 5.8%, ≥ 40: 9.7%.

Team Leader Comments:

- **The risk of expulsion is clearly highest in the first year of use.**
- **Given the consideration that IUD insertion in the smaller uterus of a nulliparous woman might be more prone to expulsion, it is of interest that the rate appears higher in parous women.**
- **The rate of expulsion appears fairly consistent across the two inserters.**
- **The trend of increasing expulsion with BMI is of interest and deserves further consideration in the recommended postmarketing study.**

8.3.5 Ovarian cysts

Ovarian cysts were ascertained only when women complained of symptoms; routine ultrasound surveillance was not performed. Sixty Liletta subjects (3.4%) reported ovarian cysts, six of whom (0.3%) discontinued due to this AE (one additional woman discontinued due to an ectopic pregnancy but a ruptured ovarian cyst was also noted at surgery). Assessed in various subgroups, ovarian cysts were more common in white women and women aged 18-30; rates were similar by parity and decreased as BMI category went from "normal" to "morbidly obese."

8.3.6 Pap Smears

Subjects had Pap smears at Screening and then only as required when clinically indicated based on ASCCP guidelines. At baseline, 93.6% of subjects had a normal Pap; at Month 12, only 244 women (13.9%) had Pap smears; of these 85.7% were normal; 5.3% were ASCUS-HPV positive, and 6.1% were LSIL. There were no HSIL or ASC-H results. At Month 24, 241 women (13.8%) had Pap smears; of these 88.4% were normal, 1.7% were ASCUS-HPV positive, and 6.5% were LSIL. There were no HSIL or ASC-H results.

Team Leader Comment:
The slight decrease in normal Pap smears is not unexpected over time, as Paps would be most likely to be obtained when a woman had a previous abnormal result or other indication for a repeat assessment. There is no signal of higher grade abnormalities of concern.

8.3.7 Return to Fertility

Women who discontinued the study and desired pregnancy were followed for up to12 months. Overall, 68 women were followed and 59 (86.8%) became pregnant by the 12-month follow-up; the rate was similar for parous and nulliparous women. The median time to conception was 92 days after IUS removal; about half of all pregnancies occurred in the first three months post-removal, and 99% within the first nine months.

8.4 SPECIAL SAFETY STUDIES

8.4.1 Endometrial histology and ultrasound

Endometrial thickness based on transvaginal ultrasound was studied in a subset (N=59) of subjects in Study L102, for European filing purposes. Thickness was measured at baseline and Month 12; however, the study visits were not timed so as to ensure that assessments were done in the luteal phase; therefore the data obtained during the luteal phase were insufficient to allow an informed comparison. Little change was observed from baseline to Month 12.

8.5 LABORATORY TESTING & VITAL SIGNS

Dr. Davis' review discusses these evaluations; there were no notable changes during the study on any of the parameters evaluated.

8.6 DATA FROM MENORRHAGIA STUDY

This study involved a different population (women with menorrhagia, virtually all were parous) and indication (treatment of heavy menstrual bleeding), so safety data are reviewed only at a high level. Subjects were randomized to the Levosert IUS (comparable to Liletta) or to Mirena and studied for 12 months; a 25% subset was selected to continue into the extension phase, which ran to 36 months. The study used the THI-001 inserter.

No deaths, ectopic pregnancies or cases of PID or uterine perforation were reported in either treatment arm. No SAEs were reported in the Mirena arm; while five were for Levosert. These included two potentially related to treatment: pregnancy and ovarian cysts. The pregnancy was diagnosed about two months after IUS insertion; however, the IUS string was not found on examination, and ultrasound did not detect the IUS, so it was believed that the pregnancy occurred after an unnoticed IUS expulsion. The subject with an SAE of ovarian cysts had bilateral cysts about 2.5 cm each detected at routine sonography about nine months post-insertion. She underwent laparoscopy to rule out malignancy and the cysts resolved several months later.

Overall, 24 subjects (17%) randomized to Levosert and 21 (15%) randomized to Mirena discontinued the study prematurely. The majority of discontinuations in each arm occurred in the first year. One Levosert subject discontinued due to an AE (4% of all discontinuations), while three Mirena subjects (14%) did so. There were no discontinuations in either arm due to pregnancy. Six Levosert subjects (25%) and six Mirena subjects (29%) discontinued due to IUS expulsion.

Team Leader Comment:
There were no unexpected safety signals noted in the LEVOSERT study.

8.7 POSTMARKETING SAFETY FINDINGS

No postmarketing safety data are available for Liletta because it had not been approved anywhere at the time of submission. The European IUS approved for menorrhagia as Levosert is owned by another company, and has been marketed in two European countries since spring 2014. The Applicant provided the following post-marketing information on Levosert: (b) (4) units have been sold and six spontaneous AE reports have been received; two of expulsion, one of uterine infection, two of placement failure and one of difficult placement. Several were associated with off-label use.

8.8 SAFETY UPDATE

A 120-day Safety Update Report was submitted on August 27, 2014, covering the period from July 13, 2013 through May 30, 2014. The safety update included new safety information from ongoing Study L102, and a clinical study report for Study L104, evaluating the performance of the to-be-marketed THI-002 inserter, which is reviewed in Section 7.4.5.

Notable AEs reported in the safety update or a subsequent 15-day safety report dated January 15, 2015 include three ectopic pregnancies, 13 expulsions, 12 cases of ovarian cysts (one leading to premature discontinuation), eight additional SAEs and 22 additional AEs leading to discontinuation. There were no additional cases of death, PID/endometritis, or uterine perforations.

Overall, the Applicant concluded that there were no new safety concerns.

Team Leader Comments:

- **The pregnancy, ectopic pregnancy, expulsion and AE rates in the body of this review have been updated with the additional cases reported in the Safety Update.**
- **I concur that no new safety signals were identified in the Safety Update.**

8.9 SPECIAL ISSUES RELATIVE TO THIS NDA

8.9.1 THI-002 inserter

The to-be-marketed inserter has been studied in a single short-term study, Study L104. Details of the study are provided in Section **Error! Reference source not found.**. In summary, Study L104 provided the following information:

- The "successful insertion" rate was 99% (95% on the first attempt)
- However, 19 insertions were rated as "difficult"

- After sounding the uterine cavity, there was difficulty passing the inserter through the cervical canal in 13 cases, with problems including "kinking" of the inserter tube and problems with the flexibility of the tube
- There was recurrent difficulty loading the IUS into the inserter in 4 cases
- In 4 cases, the IUS pulled out when the inserter was withdrawn

Therefore, while I believe that Study L104 supports the overall safety and usability of the THI-002 inserter, there is a need for additional information about the performance of the THI-002 inserter that should be collected post-approval. A program modeled after the European AMPS (active postmarketing surveillance study) for Levosert (LNG-IUS) is recommended (see Section 13.4).

8.10 OVERALL ASSESSMENT OF SAFETY FINDINGS

The clinical safety database for Liletta based on the phase 3 study included 1,751 subjects who provided over 39,108 28-day cycles of exposure. The Applicant provided the number of cycles the Division had requested, all in US subjects, and also enrolled a notable proportion of nulliparous and overweight/obese women. A total of 383 women completed three years of use through the Safety Update.

There was a single death in the clinical trials, a suicide, which is potentially associated with treatment, given the known association of progestins and depression. However, overall, the risk of suicide attempts does not appear to be outside the background rate.

SAEs occurred in 2.6% of women; the most common SARs (at least possibly related to Liletta) are exacerbation of psychiatric conditions, ectopic pregnancy, suicidality, and ovarian cysts. There were two venous thromboembolic events that were not associated with other reported risk factors, and therefore, should be considered possibly related.

Device expulsion was the most common AE associated with premature discontinuation, as this was required by protocol in the case of expulsion. Other AEs leading to early discontinuation (> 1%) were bleeding complaints, acne, mood disorders and dysmenorrhea. Common AEs (≥ 5%) included vaginal infections, acne, headaches, nausea/vomiting, dyspareunia, abdominal, breast and pelvic pain, and mood disorders. Five of the six reported pregnancies were ectopic, for an overall frequency of 0.2% of subjects. IUS-related AEs such as PID, ovarian cysts, perforation and expulsion of the devices occurred at rates that do not appear excessive in comparison to other approved LNG IUSs.

While there are some minor differences in individual AEs by subgroups defined by parity, inserter or BMI, it is difficult to determine whether these represent true differences or occur by chance, particularly because the time at risk is not comparable for the two inserter groups.

Overall, the safety profile of Liletta appears acceptable to support approval for prevention of pregnancy for up to three years in women (b) (4).

9. Advisory Committee Meeting

An Advisory Committee meeting was not requested for this application, as it represents a contraceptive product very similar to currently marketed products.

10. Pediatrics

The Applicant and the Division initially believed that PREA would not apply to this NDA because it did not contain a new active ingredient, indication, dosage form, dosing regimen or route of administration. However, it was subsequently recognized that the indication is not identical to that of Mirena, because Liletta is currently only requesting labeling for three years of use, while Mirena is labeled for five years of use. As a contingency plan, the Applicant requested a waiver of pediatric studies in premenarcheal females (b) (4) because the indication is not relevant to this population. The Applicant also requested a waiver of studies in postmenarcheal females (b) (4) because safety and efficacy data for this population can be extrapolated from the adult data. The Division concurred. The Pediatric Review Committee (PeRC), on December 3, 2014, (b) (4)

11. Other Relevant Regulatory Issues

The Applicant certified that it did not use any debarred investigators. The Applicant also certified that all investigators submitted financial disclosure information and that none had anything to disclose.

The Office of Scientific Investigation (OSI) inspected two sites for Study L102. The sites were chosen based on considerations that included the number of subjects enrolled and lack of previous inspections.

Dr. Eisenberg's site (108) enrolled 186 subjects, and received a No Action Indicated (NAI) evaluation following review of 40 subjects' records. The study appeared to have been conducted adequately and the data appear acceptable.

Dr. Westhoff's site (141) enrolled 119 subjects, and received a classification of Voluntary Action Indicated (VAI), following review of 24 subjects' records. A Form 483 was issued at the conclusion of the inspection. Specific concerns included lack of a pregnancy test for one subject, and incomplete pelvic exams for several subjects. In addition, deficiencies included an uncollected LNG sample for one subject at one visit, and unmonitored temperature of storage systems for LNG samples and IUSs. More significantly, AEs were not always appropriately reported or recorded, including an SAE for Subject 2071 and AEs of dizziness, clamminess and a vaso-vagal reaction with a period of unconsciousness post-insertion for Subject 2112, which was reported only as nausea on the source document. However, overall, the inspector stated that the study appeared to have been conducted adequately and the data appear acceptable.

Team Leader Comment:

- **Dr. Davis has provided details on these two cases in his review. The SAE for Subject 2071 was related to a domestic assault, and is not drug-related. For Subject 2112, the CRF was amended to change the AE from "nausea" to "vasovagal reaction," which occurred after the subject left the office following the IUS insertion. The subject denied actual loss of consciousness. I concur that neither significantly impacts the AE profile for Liletta.**

Roy Blay, Ph.D., from OSI made the following overall assessment and general recommendations in his review dated January 7, 2015:

The clinical sites of Drs. Eisenberg and Westhoff were inspected in support of this NDA. Dr. Eisenberg was not issued a Form FDA 483, and the final classification of this inspection was No Action Indicated (NAI). Dr. Westhoff was issued a Form FDA 483; however, the deficiencies noted were isolated and would not appear to have adversely affected safety or efficacy considerations, and the final classification of this inspection was Voluntary Action Indicated (VAI). The data generated by these clinical sites appear adequate in support of the respective indication.

12. Labeling

The Applicant submitted the proposed proprietary name (b) (4), which was found to be unacceptable by the Division of Medication Error Prevention and Analysis (DMEPA). The alternative proprietary name Liletta was found acceptable by DMEPA on December 4, 2014.

Carton and container labeling was reviewed, revised and found acceptable by DMEPA, the Office of Prescription Drug Promotion (OPDP) and the CMC reviewer.

The label was submitted in the format prescribed by the Physician Labeling Rule (PLR); labeling for the similar products, Mirena and Skyla, is already in PLR format. The package insert and patient labeling were reviewed by the review disciplines, DMEPA, OPDP and the Division of Medical Policy Programs (DMPP) Patient Labeling Team, and their comments were conveyed to the Applicant. Labeling pertaining to safety of MRI scanning was requested and reviewed by CDRH; language was included in the package insert and patient labeling.

Specific issues discussed during labeling negotiations included the determination of adverse reactions from the AE data, and updating labeled information with data from the 120-day Safety Update, including the cumulative 3-year life table pregnancy rate. Agreement on labeling was reached on February 25, 2015.

13. Recommendations/Risk Benefit Assessment

13.1 RECOMMENDED REGULATORY ACTION

I recommend that Liletta receive an Approval action.

13.2 RISK BENEFIT ASSESSMENT

The efficacy of Liletta in prevention of pregnancy is acceptable throughout the requested three-year treatment duration. Efficacy was very similar regardless of parity or BMI. About 1/3 of all pregnancies occurred in the face of partial or total expulsion; thus the contraceptive efficacy of the product when correctly situated appears very high.

The risks associated with this IUS are those well-characterized in association with hormonal IUSs, and the safety data do not suggest that these risks are higher for this product. The safety data on the large proportion of nulliparous women and women of high BMI who were enrolled in the phase 3 study suggests that Liletta has an acceptable safety signal when used in women broadly representative of the target population.

With respect to inclusion of the THI-002 inserter, which was not evaluated in the phase 3 trial, I conclude that sufficient evidence of safety and functionality was provided in the phase

1 study L104 to support approval. However, Study L104 was conducted at six sites that are known to be experienced with IUS insertions and associated adverse events. Although the study was conducted as requested by the Division, it provided a limited evaluation of the functionality of the THI-002 inserter, because it enrolled a relatively small number of women (100), and had only 24 hour follow-up in person and then a follow up phone call about 7 days post-insertion to assess any further adverse events. The study did suggest that, despite the redesign of the inserter, some problems remain regarding difficult insertions, kinking of the inserter tube and the IUS pulling out when the inserter is withdrawn. For this reason, I recommend that a post-marketing study of the inserter be conducted as a post-marketing commitment (see Section 13.4), to help evaluate whether labeling and experience with IUS insertions mitigates these problems.

13.3 RECOMMENDATION FOR POSTMARKETING RISK MANAGEMENT ACTIVITIES

I do not believe any specific risk management activities, beyond standard labeling and postmarketing safety monitoring, are needed.

13.4 RECOMMENDATION FOR OTHER POSTMARKETING STUDY REQUIREMENTS AND COMMITMENTS

I concur with Dr. Davis that it is advisable to request additional data collection in the post-marketing period to evaluate further the THI-002 inserter. Similarly, the MHRA requested such a study to support its approval of the THI-002 inserter for use with (b) (4), as the (b) (4) phase 3 trial did not use the THI-002 inserter. A program modeled after the European AMPS (active postmarketing surveillance study) for (b) (4) is requested, to focus on the following data:

- characterizing ease of insertion, insertion difficulties, and failed insertions
  - use of local anesthesia
  - use of rigid dilation
  - use of ultrasound guidance
- adverse events (AEs) such as pain, vasovagal events, excessive bleeding and uterine perforation during insertion and before the subject leaves the healthcare facility after insertion
- subsequent AEs such as pain and bleeding in the 7-14 days after IUS placement
- any additional AEs reported at the follow-up visit
- expulsions, infections, and other more serious AEs that may be delayed but related to the insertion procedure or IUS

Similar to the AMPS study, approximately 1,000 women should be studied from a variety of clinical settings (private practice, family planning clinics, and teaching institutions). The enrolled subjects should be followed for a minimum of three months to monitor for expulsion, perforation and infection because these two adverse events are more common during this time period and may be related to the inserter or the insertion process. IUS removal data is not of primary importance and does not need to be obtained unless the IUS

was removed specifically due to an insertion-related AE. Data on the utilization pattern of Liletta is also not required.

I also recommend that the study enroll representative proportions of nulliparous users and obese women to reflect the overall user population for the labeled indication. In addition, for women who have the IUS inserted post-partum, data should be collected on time since delivery/pregnancy termination, and on whether they are lactating.

The Applicant agreed to the PMC and committed to the following milestones for this PMC:

Final Protocol Submission: 2/28/2016
Study/Trial Completion: 2/28/2018
Final Report Submission: 2/28/2019

13.5 RECOMMENDED COMMENTS TO APPLICANT

None

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LISA M SOULE
02/25/2015

AUDREY L GASSMAN
02/25/2015