# CLINICAL REVIEW

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| Application Type | NDA |
| Application Number(s) | 206229 |
| Priority or Standard | Standard |
| Submit Date(s) | April 29, 2014 |
| Received Date(s) | April 29, 2014 |
| PDUFA Goal Date | February 28, 2015 |
| Division / Office | Bone, Reproductive and Urologic Products (DBRUP)/Office of Drug Evaluation III (ODE III) |
| Reviewer Name(s) | Daniel Davis, MD, MPH |
| Review Completion Date | February 23, 2015 |
| Established Name | Levonorgestrel (LNG)-releasing intrauterine system (IUS) |
| (Proposed) Trade Name | Liletta |
| Therapeutic Class | Progestin-containing intrauterine device |
| Applicant | Medicines360 Inc. |
| Formulation(s) | Intrauterine device |
| Dosing Regimen | Insert into uterine cavity for up to 3 years of contraception |
| Indication(s) | Contraception |
| Intended Population(s) | Women of childbearing age |

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# 1 Recommendations/Risk Benefit Assessment

## 1.1 Recommendation on Regulatory Action

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.

## 1.2 Risk Benefit Assessment

The PI for LNG-IUS (hereafter referred to as Liletta) was derived from the data obtained from the phase 3 clinical trial L102 (performed entirely in the US) which included women 16 to 45 years of age in whom a Liletta insertion was at least attempted. Cycles in which back-up contraception was used were excluded from the primary efficacy analysis unless a pregnancy occurred in that cycle. For data through December 19, 2014:

- the PI for Year 1 was 0.15 (95% confidence interval [CI]: 0.02, 0.55) based on a total of 17,125 28-day cycles for use
- for Year 2 was 0.41 (95% CI: 0.11, 1.05) based on a total of 12,694 28-day cycles for use
- for Year 3 was 0.00 (95% CI: 0.00, 0.98) based on 4,892 28-day cycles of use
- The cumulative PI for the 3 years was 0.22 (0.08, 0.49) based on a total of 34,711 28-day cycles (2,670 woman-years of use)
- The life table calculation for the cumulative 3-year pregnancy rate is slightly higher at 0.55 (0.24, 1.23)

In all of the original NDA submission PI calculations for the overall Liletta modified intent to treat (MITT) population (based on the pregnancies reported in the original NDA submission), the PI point estimate was ≤ 0.20 and the upper bound of the 95% CI did not exceed 0.73; therefore the difference between the upper bound of the 95% CI and the point estimate has not exceeded the maximum limit of one unit, the criterion stated in the final protocol, Version 6.0, dated August 10, 2012. The pregnancy rate data to be described in labeling includes additional pregnancies reported in the Safety Update and a January 2015 safety report.

The bulk of the Liletta safety database is derived from the analysis of data from the USA Study L102 and the phase 2/3 menorrhagia Levosert-20 Study, which was performed in Eastern Europe. The safety assessment for Liletta was based on all the women who were enrolled and had a Liletta insertion attempt. As of May 30, 2014, a total of 1,751 women, including 1,412 exposed for one year and 383 who completed the 3-year study (see Table 9), comprised the Liletta safety cohort. The safety population was generally healthy, 16 to 45-year old females, predominantly Caucasian, and requesting intrauterine contraception.



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The adverse events (AE) profile of Liletta did not give rise to any new safety concerns. There were no unusual safety signals observed with regard to IUS-related events such as complications associated with insertions, removals, expulsions or perforations, ectopic pregnancies and infections. A review of laboratory tests, vital signs, and other safety parameters that were measured also did not reveal any specific concerns.

There was one issue in this review that required special attention. This was the optimized THI-002 inserter, which was not used in the phase 3 clinical trial. Two different inserters were used in the phase 3 trial: THI-001 and (b) (4) In order to fully evaluate the safety and efficacy of the new THI-002 inserter, the Division requested additional data from a separate study M360-L104 (hereafter referred to as L104) utilizing this inserter. A review of the data from Study L104 with 100 women (57 nulliparous and 43 parous) showed a successful placement rate of 99% and no expulsions or perforations when observed for only 24 hours at which time the IUS was removed. The Applicant plans to use the THI-002 inserter with their IUS, if approved and marketed; however, it was not used for any of the 1,751 subjects in Study L102.

There were some findings that were notable and related to the IUS and/or the THI-002 inserter:

- After sounding the uterine cavity, there was difficulty passing the inserter through the cervical canal in 13 women (8 nulliparous and 5 parous).
- After placement of the IUS into the uterine cavity, in 4 women (2 nulliparous and 2 parous), the IUS came back out with removal of the THI-002 inserter.
- There was recurrent difficulty loading the IUS into the inserter in 4 women before placement.
- There was failure to place the IUS in 5 women (2 nulliparous and 3 parous) at the first attempt; placement was successful at a later date in 4 of these women (2 nulliparous and 2 parous).

Study L104 was conducted at 6 sites that are known to be experienced with IUS insertions and associated AEs. The study was conducted as requested by the Division and enrolled a relatively small number of women (100), and had only 24 hour follow-up in person and then a follow up phone call at ~ 7 days to assess any further adverse events.

Although the “successful insertion” rate was 99% (95% on the first attempt), there were 19 “difficult” insertions, which is of some concern, especially if the healthcare provider is not as experienced as the investigators were. Certain safety parameters are difficult to evaluate; for example, 3 sites with 45 subjects used no cervical anesthesia while the other three sites used some form of local anesthesia for 44 of 55 subjects. Rigid cervical dilatation for IUS placement was used for 18% of subjects, but the percentage ranged from 10 to 27% at the 6 sites. Pain scores using a VAS scale of 0 to 100 were used after sounding, after IUS placement, and before IUS removal to assess the 24 hours prior to removal. However, the study did not control for prophylactic use of pain



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medications or local cervical anesthesia, thereby confounding interpretation of the VAS pain scores. Because of the limitations of a small (N= 100) and short study (24 hours), and the notable findings listed above for the THI-002 inserter, it is reasonable that more safety data should be collected post-approval with a formal agreed-upon method. A program modeled after the Applicant's European AMPS (Active Post Marketing Surveillance) study for Levosert (LNG-IUS) is recommended, to obtain the following data:

- characterizing ease of insertion, insertion difficulties, and failures
- AEs such as pain, vasovagal events, excessive bleeding and uterine perforations during placement and soon after placement
- subsequent AEs such as pain and bleeding in the 7-14 days after IUS placement
- expulsions, infections, and other more serious AEs that may be related to the insertion procedure or IUS

Similar to the AMPS study for Levosert in Europe, 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 and infection data because these two AEs 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.

The Division also requested 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.

Overall, this reviewer concludes based on 1) the safety and efficacy data from the phase 3 L102 clinical trial submitted to this NDA, 2) Study L104 (THI-002 inserter), 3) 120-Day Safety Update submitted to the NDA on August 27, 2014, and 4) updated pregnancy and exposure data through December 19, 2014 that was submitted on February 10, 2015, that Liletta has a favorable benefit:risk profile and that the submitted data support marketing approval.

## 1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

LNG-IUS products have been on the US market since 2000 and there are currently two approved products. The indication, insertion instructions, and risks for Liletta are clear and well-defined. For these reasons, I do not believe a REMS for Liletta is needed.

### 1.4 Recommendations for Postmarketing Requirement and Commitments

Postmarketing Commitment:

As noted above, a postmarketing surveillance study with the new THI-002 inserter and focusing on the areas listed above should be performed.

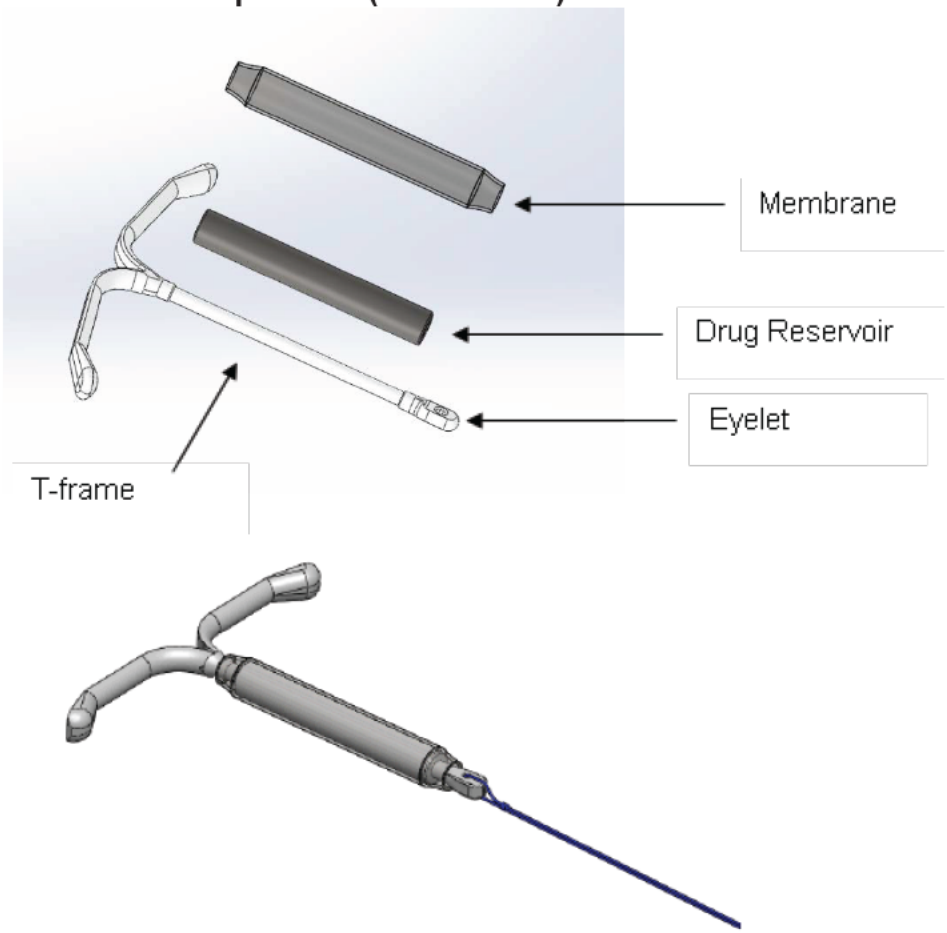
## 2 Introduction and Regulatory Background

### 2.1 Product Information

Medicines360 (the Applicant) is seeking approval for a low-dose, levonorgestrel (LNG)-releasing intrauterine delivery system (IUS) for contraception. The proposed indication is the prevention of pregnancy for up to 3 years.

This LNG IUS (referred to as Liletta) is composed of (1) the T-frame (2) a drug [(b) (4)] of 52 mg of [(b) (4)] LNG, and (3) a covering outer membrane. See Figure 1.

**Figure 1: Liletta Components (not to scale)**



The Liletta drug product is a LNG-releasing IUS. The drug product consists of a T-shaped polyethylene frame (T-frame) with a (b) (4) reservoir (drug reservoir) around the vertical stem. The drug reservoir consists of a cylinder made of a mixture of LNG and polydimethylsiloxane (PDMS) formed from silicone base, tetra-n-propyl silicate, and stannous octoate. The drug reservoir is covered with a PDMS membrane. The T-frame has an eyelet at one end of the vertical stem and two horizontal arms at the other end. The low-density polyethylene of the T-frame is compounded with barium sulfate, which makes it radiopaque. A blue polypropylene monofilament removal thread is attached to the eyelet at the end of the vertical stem of the T-frame to aid in identification and removal of the IUS.

**Inserter:**

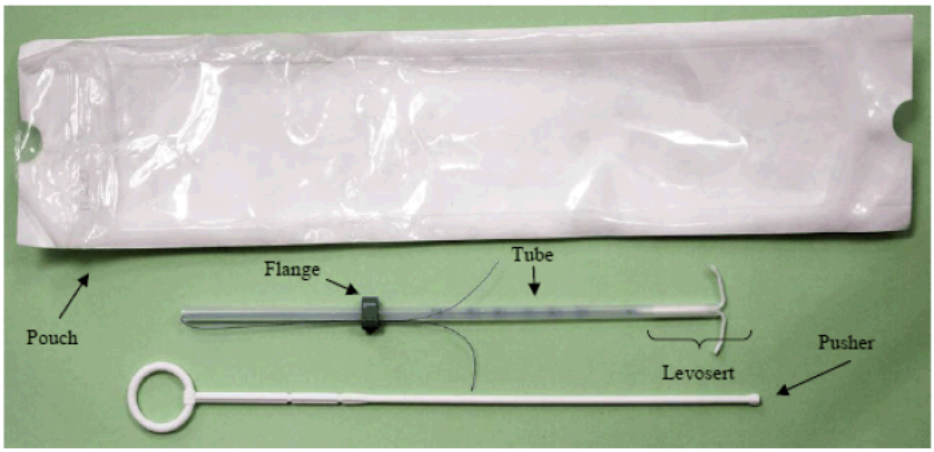
Each Liletta is placed within an inserter tube that is used for insertion into the uterus. The inserter tube consists of a high-density polyethylene (HDPE) that is (b) (4) and is supplied with a polyurethane flange and (b) (4)

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 optimize the insertion process by decreasing the number of preparatory steps prior to insertion. The (b) (4) inserter was a two-handed model referred to as THI-001, which was used on about 800 subjects in phase 3. Based on feedback from investigators about patient discomfort and difficult insertions; however, the trial was paused (b) (4) (b) (4) (b) (4) (b) (4) the Applicant has opted to market Liletta with a modified two-handed inserter, THI-002. As noted, the Division requested that the Applicant conduct a clinical study to characterize the safety and performance of inserter THI-002 in 100 healthy female subjects age 18-45; this was done in Study L104. Details of Study (b) (4) and L104 are found in Sections 7.4.5.1.1 and 7.4.5.1.2.

**Container Closure:**

The Liletta and inserter tube will be packaged in a pouch constructed of (b) (4) A diagram of the Liletta, inserter, and pouch follows in Figure 2.

**Figure 2: Liletta with Inserter and Pouch (not to scale)**




**Source: Applicant's Description and Composition figure 3.**

**Medical Reviewer's Comments**

- The actual T-shaped IUS that was used in the pivotal trial for this NDA is the same as the to-be-marketed product. (b) (4)
- It is of note that the LNG-IUS used in the (b) (4) (b) (4)
  - Liletta is a (b) (4) component in the shape of a "T" with two side arms (width) and a vertical stem (length) with a loop at the bottom (Figure 1). The T-frame is 32 mm by 32 mm (width x length). The reservoir is mounted on the vertical arm of a T-shaped plastic frame and is covered with a release rate-controlling membrane. By comparison, the approved copper IUS, ParaGard, measures 32 by 36 mm and contains (b) (4) of exposed copper. Mirena measures 32 by 32 mm and is larger than the approved Skyla, which measures 28 mm by 30 mm.
  - Liletta is regulated as a drug product as are all IUSs. However, the inserter for the IUS is treated as a device, necessitating a consultative review by the Center for Devices and Radiologic Health (CDRH). The actual IUS is evaluated by ONDQA for quality and manufacturing.

## 2.2 Tables of Currently Available Treatments for Proposed Indications

Currently, there are three FDA-approved IUSs available for intrauterine contraception. These are Mirena, Skyla and the copper-containing ParaGard T 380A: Mirena is recommended for women "who have had at least one child." The ParaGard and Skyla labels do not specify any parity restriction but have been used in nulliparous women.

1. The ParaGard® T 380A (NDA 018-680) was originally approved in 1984. It is currently approved for intrauterine contraception for up to 10 years. The

pregnancy rate in clinical studies of the ParaGard IUS has been less than 1 pregnancy per 100 women each year.

2. Mirena (NDA 021-225), a LNG IUS, was first approved for marketing in Finland in 1990 and has been approved in the US since 2000. It is currently approved for (1) intrauterine contraception for up to 5 years and (2) the treatment of heavy menstrual bleeding for women who choose intrauterine contraception as their method of contraception. The reported 12-month Pearl Index for Mirena is (b) (4) per 100 women (0.2%) and the cumulative 5-year value is (b) (4)
3. Skyla (NDA 203-159), another LNG IUS, was approved in January 2013 with a 3-year pregnancy rate of (b) (4) per 100 women.

## 2.3 Availability of Proposed Active Ingredient in the United States

LNG, the active drug component of Liletta, has a long history of use in combination with estrogen for gynecologic and contraceptive indications in the US. These indications include contraception (oral, transdermal, and intrauterine use), the treatment of heavy menstrual bleeding and the treatment of vasomotor symptoms due to menopause.

**Medical Reviewer's Comment**

- It is of note that the LNG-IUS used in the menorrhagia Levosert-20 Study was approved in 2013, but not yet marketed, in (b) (4) .

## 2.4 Important Safety Issues with Consideration to Related Drugs

Intrauterine contraceptive devices as a general class have the following safety issues:

- sexually transmitted infection and pelvic inflammatory disease with the subsequent risk of infertility
- uterine perforation or expulsion (partial or complete)
- ectopic pregnancy
- pregnancy loss or septic abortion if a pregnancy occurs with an IUD in situ
- ovarian cysts

## 2.5 Summary of Presubmission Regulatory Activity Related to Submission

Liletta was studied under Medicines360's IND 105,836, opened on November 21, 2009.

In previous communications with the FDA (Pre-IND meeting of September 10, 2009, Type C Guidance meeting held June 26, 2012 and the Pre-NDA meeting dated September 17, 2013), the Division confirmed that the product labeling for Liletta may be entirely supported by efficacy and safety data from a single pivotal phase 3 trial (M360-L102) as well as information from the public domain (i.e., a 505(b)(2) approach). Additionally, the Division agreed that Liletta could be approved prior to completion of the

planned 5-year duration of the study, with the indication and labeling to reflect the actual duration of use for which data were submitted as long as a minimum of 200 subjects reached the maximum duration of use and acceptable efficacy was demonstrated. Originally the Applicant [redacted] (b) (4) the Division recommended that they wait and seek a 3-year approval, which they did. Medicines360 obtained sufficient data to support the efficacy and safety of Liletta for reversible contraception for three years of use on July 12, 2013 and these data are the basis for the approval of this NDA submission.

**Medical Reviewer's Comment**

- The Applicant [redacted] (b) (4) of contraception; after hearing the Division's recommendation, [redacted] (b) (4) sufficient data for a 3-year approval while continuing the L102 clinical trial for 5 years for each subject that desired to continue use of the IUS.

The primary objective of Study M360-L102 was to establish the efficacy of Liletta as determined by the Pearl Index (PI) over a 3-year use. A secondary objective was to continue the study for 5 years of IUS use for contraception.

A Type B Pre-NDA Meeting held on September 17, 2013 discussed the format and content of the NDA for Liletta. During the discussion, the Division made the following key comments or agreements:

- A 505(b)(2) NDA submission appears reasonable.
- The proposed label should be submitted in the PLR format.
- Upon initial consideration, it appears that the Pediatric Research Equity Act (PREA) does not apply to this product. However, the final determination will be made during the review cycle.
- The Division agreed that Integrated Summaries of Safety and Efficacy (ISS and ISE) are not required because a single phase 3 safety and efficacy study was conducted.
- The Division agreed with the Summary of Key Agreements with one exception: because the inserter proposed for use with the to-be-marketed product was not one of the two evaluated in the phase 3 study, careful consideration will be given to information about the to-be-marketed inserter and to the data from the subset of subjects who experienced the THI-001 inserter.
    - The Division requests that safety and efficacy data be presented separately for the two inserter subgroups to allow for evaluation of whether the different inserters appear to impact safety or efficacy.
    - A pooled analysis should also be provided. The specific (sub)population used for the efficacy analysis to support labeling will be a review issue.
- As discussed in the June 2012 meeting, the application does not appear to meet the criteria for priority review, but this determination will be made after the NDA is submitted.
- The Division found the proposed eCTD submission plan acceptable.

- The Division also requested that the Sponsor address IUS-specific safety concerns including perforations, expulsions (partial and total), pelvic infections (uterine [endometritis] and more generalized [Pelvic Inflammatory Disease]), ectopic pregnancies, ovarian cysts, dysmenorrhea, etc.
    - Data pertaining to insertion and removal (failed insertions and removals, broken strings, and reasons for removal, as well as data on ease/pain of insertion and removal from the healthcare provider and patient perspective, respectively, if obtained) is needed and should be stratified by inserter used.
    - Data on return to fertility after discontinuation of the IUS should be presented as available (i.e., in women who discontinued with the intent of conceiving).
- It appeared that the efficacy and exposure dataset will be adequate to support an application for a three-year indication; however, the final determination will be made during the review cycle.
- The inclusion of secondary efficacy analyses in older women and subgroups based on age, ethnicity, parity and BMI was acceptable. The Division will also evaluate the efficacy data in subgroups based upon inserter-type. Should a marked discrepancy in effectiveness be apparent, further exploration may be needed, including presentation of Pearl Indices and 95% CIs for each subgroup.
- The Division did not agree that the single primary efficacy consideration is the [redacted] (b) (4) Pearl Index. The acceptability of the Year 1, Year 2, Year 3 and cumulative three-year Pearl Indices will all be considered in evaluating efficacy. Failure to demonstrate an acceptable Pearl Index at any of these intervals would be a significant review issue.
- The Division agreed with the data cutoff for the database lock for the 120-day safety update to be set at 3 months prior to the due date based on the NDA submission date. This data cutoff date in this ongoing study represents 6 additional months from the data cutoff date (i.e., July 2013) that is set for the NDA submission.
- The Division asked the Application to clarify how bleeding data were ascertained in each of the 3 years of the clinical trial.
- Concerning the Applicant's proposal to use an optimized 2-handed THI-001 inserter (designated as THI-002) that is very similar to the inserter used in the first 760 subjects enrolled in the phase 3 clinical trial, the Division had several comments:
    - Ideally, the final finished combination product should be studied in phase 3. The extent to which this to-be-marketed optimized inserter (THI-002) is supported by data obtained from use of the THI-001 inserter in the phase 3 trial will be determined during the NDA review.
    - The Division was also interested in the reason [redacted] (b) (4)

- CDRH will be involved in the review of the to-be-marketed inserter and the extent to which the Applicant has characterized the potential impact of the modified inserter on the performance of the IUS. A long list of specific types of information was given to the Applicant that would assist in the NDA review relative to the approval of the optimized THI-002 inserter.
- In addition, regarding manufacturing practice for combination products, the Applicant was reminded that combination products are subject to 21 CFR Part 4 – Current Good Manufacturing Practice Requirements for Combination Products.

## 2.6 Other Relevant Background Information

### 2.6.1 Information Requests (IR)

On September 15, 2014, basic data on screen failures was requested by the Division

On November 5, 2014, an information request (IR) from the CMC reviewer was sent to the Applicant for 1) *in vitro* drug release data at several time points for each batch tested, and 2) to "add the proposed detailed description to the DP Specification". The Applicant's response was received on November 20th in the EDR.

On November 10, 2014, an IR from the CDRH reviewer was sent to the Applicant. The Applicant's response was received on November 26th in the EDR.

On December 10, 2014, an IR from the clinical reviewer asked for the Investigator Brochure which was submitted to the EDR on December 16trh.

On January 2 and 7, 2015, an IR was sent to make several minor updates to the container and carton labeling and the patient information booklet, and categorize the LNG-IUS in terms of compatibility with MRI (magnetic resonance imaging). The Applicant responded on January 26th.

**Medical Reviewer's Comment**

- The IRs from the Division were answered by Applicant in a timely manner.

### 2.6.2 Division of Medication Error Prevention and Analysis (DMEPA)

Label and Labeling Review:

On November 5, 2014, Denise Baugh, PharmD, BCPS, completed her review of the Applicant's submissions from April 30 and October 3, 2014. The pouch label, carton insert, patient booklet cover labeling, patient reminder card and patient reminder sticker were reviewed for vulnerabilities to medication errors. Consistency with the approved labels for Mirena® and Skyla was considered. Her conclusion follows:

> "Based upon 1) our review of the proposed label and labeling; 2) our review of the recommendations for Skyla and Mirena; and 3) the retrieval of expired drug errors and monitoring errors involving Skyla and Mirena, we conclude that improvements can be made to the label and labeling to minimize errors. We recommend these improvements be implemented prior to approval of NDA 206229."

On January 2, 2015 a memo was sent to the Applicant listing all of the specific recommendations based on this DMEPA review.

Proprietary Name Review:

On May 20, 2014 the Applicant submitted the proprietary name (b) (4) for their product. On August 12, 2014, DMEPA Deputy Director Kellie Taylor sent a letter to the Applicant stating, "We have completed our review of the proposed proprietary name, (b) (4) and have concluded that this name is unacceptable for the following reasons." (b) (4)

On December 2, 2014 Denise Baugh completed a review for the newly submitted proprietary name Liletta for the Applicant's product. The 27-pg review concluded that the proprietary name Liletta is acceptable.

**Medical Reviewer's Comment**

- I concur with the two Proprietary Name reviews and the label and labeling review noted above and the final labeling reviews by all the disciplines.

### 2.6.3 Good Clinical Practice Assessment Branch, Office of Scientific Investigations

On March 7, 2014, the Division requested the Office of Scientific Investigations (OSI) to audit 2 sites from Study L102 to insure data integrity. These sites, # 108 (D Eisenberg, MD - St. Louis) and # 141 (C Westhoff, MD - New York City), enrolled 186 and 119 subjects, respectively.

Dr. Westhoff's site enrolled 119 subjects, and following review of 24 subjects' records received a final classification of Voluntary Action Indicated (VAI) in a letter from OSI on January 7, 2015. A Form 483 was issued at the conclusion of the inspection in September 2014. 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 a serious adverse event (SAE) for Subject 2071 [December 5, 2012], and AEs of dizziness, clamminess and a vasovagal reaction

with a period of unconsciousness post-insertion for Subject 2112, which was reported only as nausea on the source document.

**Medical Reviewer's Comments**

- Subject 2071: a 30 year old Hispanic G3P1 woman; this SAE was due an assault by her estranged husband resulting in bilateral wrist lacerations that required hospitalization, surgery, and physical therapy follow up. I concur that the SAE was not related to the IUS. She reported a total of 9 AEs starting 5 weeks after the IUS insertion: this included a mild headache, mild fainting feeling, vasovagal symptoms, common cold and the serious wrists lacerations.
- Subject 2112: A follow-up report on February 2, 2015 from the Principal Investigator Dr. Carolyn Westhoff stated the following: this 19 year old G0P0 subject did experience nausea after an easy insertion of Liletta, but had stable vital signs and was discharged from the clinic at the hospital. She took the elevator to the lobby and vomited into a waste container. Hospital security took her to the pediatric emergency room (ED) for evaluation; the ED doctor noted loss of consciousness (LOC); Dr. Westhoff joined the subject in the ED to facilitate her assessment. LOC was not recorded by the investigator because LOC was never observed and the subject denied LOC on further questioning. Her symptoms were consistent with a vasovagal reaction.

  Follow up visits at Months 1 and 3 were normal and no AEs were recorded. The amended CRF changed the AE from "nausea" to "vasovagal reaction."

Dr. Eisenberg's site enrolled 186 subject and 133 remained enrolled at the time of the inspection in October 2014. Records of 40 subjects were reviewed. A Form FDA 483 was not issued at the conclusion of the inspection. "The study appeared to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication." A NAI (no action indicated) letter was sent to the site on December 15, 2014.

# 3 Ethics and Good Clinical Practices

## 3.1 Submission Quality and Integrity

The Applicant states that phase 2 and phase 3 clinical trials were conducted in accordance with the International Conference on Harmonization, the principles of the Declaration of Helsinki, and all applicable national regulations valid at the time the studies were performed. The protocols and protocol amendments were reviewed and approved by Independent Ethics Committees or Institutional Review Boards.

## 3.2 Compliance with Good Clinical Practices

The Applicant attests that the pivotal phase 3 clinical trial and the supportive clinical trials were conducted in compliance with Good Clinical Practice.

### 3.3 Financial Disclosures

Medicines360 submitted a signed Certification: Financial Interests and Arrangements of Clinical Investigators form (Form FDA 3454) in compliance with 21 CFR part 54 for Study L102. They also provided a Financial/Certification Disclosure Table for each study.

All investigators and sub-investigators in the phase 3 Study L102 filed Financial Certification/Disclosure Forms and all marked "No" under Disclosable Information.

**Medical Reviewer's Comment**

- Medicines360 is a small company in California and has developed only one product, namely the LNG-IUS for this NDA submission. Many of the investigators for the phase 3 clinical trial have been involved with other contraceptive trials, but all investigators declared that they did not have a financial interest in Medicines360 or receive special incentives to enroll subjects in the clinical trial.

## 4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

### 4.1 Chemistry Manufacturing and Controls (ONDQA)

ONDQA

The CMC reviewer (Nina Ni) for this application concluded the following in her draft review dated December 18, 2014:

- The Applicant has not provided sufficient information to assure identity, strength, purity, and quality of the drug product.
- The Office of Compliance (OC) made an overall acceptable recommendation for the manufacturing facilities on February 2, 2015.

ONDQA/Biopharmaceutics

The ONDQA/Biopharmaceutics reviewer Kelly Kitchens, PhD reviewed the submitted data that focused on evaluation of the development of the drug release method and drug release data for the proposed drug release acceptance criteria. Drug release data from 7 clinical and stability batches were included for setting the acceptance criteria for the product, including release data from stability testing of these batches stored at long-term conditions (25°C / 60% RH). She has recommended approval based on her evaluation.

OPF (Office of Process and Facilities)- initial manufacturing (CGMP/Facilities)

OPF did receive the official documentation and approvals from the FDA inspections that were performed.



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**Medical Reviewer's Comment**

- The different FDA groups that are responsible for evaluation of the manufacturing, quality, stability of the IUS, and all the technical methods used to establish these parameters, have recommended approval of the NDA from their respective disciplines. I concur with their conclusions.

## 4.2 Clinical Microbiology

The Product Quality Microbiology Review by Denise A. Miller was completed on January 23, 2014. From the product quality microbiologic perspective, approval was recommended.

## 4.3 Preclinical Pharmacology/Toxicology

The Applicant did not conduct nonclinical toxicology studies on LNG (the active pharmaceutical ingredient [API] in Liletta) for this NDA submission. Krishan Raheja, D.V.M., PhD, stated in his December 10, 2014 review:

> "In accordance with discussion between the sponsor and the Division in the Pre-NDA meeting, no preclinical studies were recommended by the Division or conducted by the sponsor. All desired studies to establish the safety of the active ingredient of (b) (4), LNG and materials used in the manufacture of the drug reservoir and inserter have been supported by either reference to published literature or to studies for which sponsor has right of reference. Based on a review of the referenced material along with the long-term clinical use of the active ingredient, the preclinical requirements for determination of the safety of (b) (4) in the proposed population have been met."

Dr. Raheja recommended approval of the NDA from the pharmacology/toxicology perspective.

**Medical Reviewer's Comments**

- The Division agreed to this approach in the Pre-NDA Meeting (September 17, 2013, see response to Question 1 and Question 2 in the meeting minutes).
- I concur with the Pharmacology/Toxicology reviewer Krishan Raheja that nonclinical data support approval of Liletta for the prevention of pregnancy for up to 3 years.

## 4.4 Clinical Pharmacology

The clinical pharmacology review was started by Hyunjin Kim, PhD and transferred to Li Li, Ph.D. No dedicated clinical pharmacology studies were conducted with Liletta. LNG systemic exposure following Liletta insertion was assessed in a subset of subjects in the pivotal phase 3 study (Study M360-L102). The Office of Clinical Pharmacology/ Division of Clinical Pharmacology 3 (OCP/DCP3) 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. No postmarketing requirements or commitments are recommended.

**Medical Reviewer's Comments**

- I concur with the above recommendations from the Clinical Pharmacology review completed by Li Li, PhD. On January 30, 2015.
- Additional information and comments on the mechanism of action, pharmacodynamics and pharmacokinetics of LNG IUSs are given in the following subsections.

### 4.4.1 Mechanism of Action (MOA)

The mode of action of LNG-releasing IUSs is (b) (4) LNG thickens the cervical mucus, creating a barrier to sperm penetration.

(b) (4) cervical and uterine LNG may directly inactivate sperm by reducing sperm motility and inducing premature acrosome reaction.

**Medical Reviewer's Comments**

- All the exact mechanisms of action and their relative contribution to prevention of pregnancy cannot be precisely determined.
- Section 12.1 Mechanism of Action in the approved label for Liletta is virtually the same as found with class labeling for LNG-IUSs.

### 4.4.2 Pharmacodynamics

Ovulation was not assessed in the L102 study. It is widely accepted that LNG has local progestational effects on the endometrium and the cervix. The local LNG levels stimulate histologic changes in the endometrium which include stromal pseudo-decidualization and glandular atrophy. (b) (4)

The Applicant's review of data from the literature concluded the following in their Summary of Clinical Pharmacology Studies report:

"In contrast to LNG-containing combined oral contraceptives, ovulation suppression does not play a significant role in the contraceptive effect of the LNG-releasing IUS. The effects of LNG-releasing IUS use on ovulation from studies in the literature are shown in **Table 1**. The fraction of ovulatory cycles appears to be lowest during early use, when systemic LNG concentrations are the highest (although overall very low), and then to increase with increasing duration of use. Data in the literature are consistent with what has been reported for an approved IUS (Mirena) in which 45% of menstrual cycles were ovulatory after 1 year of use and 75% of cycles were ovulatory after 4 years of use (Bayer HealthCare Pharmaceuticals Inc, 2013b). However, studies in the peer-reviewed medical literature report that despite this increase in ovulatory cycles over time, contraceptive efficacy was not reported to decrease with longer durations of use, even out to Years 6 and 7 (see Barbosa, 1995; Xiao, 1995)."

**Table 1: Effect of LNG-releasing IUS Use on Ovulation**

| Study | Duration of Use | Age (years) | Ovulation[a] |
|---|---|---|---|
| (Xiao, 1990) | 1st cycle | 25 – 34 | 5/10 subjects, Landgren type C + D |
| (Jarvela, 1998) | 3 months | Mean 32 (24 – 45) | 21/26 subjects before LNG-IUS placement[b]<br>3/26 subjects after 3 months of use[b] |
| (Jonsson, 1991) | 3 months | 26 – 40 | 27/27 subjects before LNG-IUS placement<br>6/8 subjects after LNG-IUS placement |
| (Xiao, 1995) | 6th cycle | 25 – 34 | 4/10 subjects, Landgren type C + D |
| (Nilsson, 1980)<br>25 µg/day | First 3 months | 21 – 39 | 2/7 subjects |
| (Nilsson, 1980)<br>25 µg/day | Approximately 1 year | 21 – 39 | 5/7 subjects |
| (Nilsson, 1984) | 4 years | Mean 36 | Plasma progesterone > 5 ng/mL:<br>• 7/12 (58%) of the women in the regularly menstruating group<br>• 5/8 (63%) of the women in the amenorrheic group |
| (Barbosa, 1990) | 4 years | 37.0 ± 1.3 | Regularly menstruating women:<br>• 15/17 cycles Landgren Type D<br>• 2/17 cycles Landgren Type C<br>Amenorrheic women:<br>• 2/3 women Landgren Type D<br>• 1/3 women Landgren Type C |
| (Xiao, 1995) | 6 years | 34.71 ± 1.97 | 12/14 subjects Landgren type C + D |
| (Barbosa, 1995) | 7 years | 35.0 ± 1.4 | Regularly menstruating women:<br>• 26/28 cycles Landgren Type D<br>• 1/28 cycles Landgren Type B<br>• 1/28 cycles Landgren Type A<br>Amenorrheic women:<br>• 6/7 women Landgren Type D<br>• 1/7 women Landgren Type B |

**Landgren Cycle Classifications:**

**Type A: No cyclic follicular activity, no luteal activity**
**Type B: Cyclic follicular activity, no luteal activity**
**Type C: Cyclic follicular activity, inadequate luteal activity**
**Type D: Ovulatory-like ovarian function**

[a] **Assessed by hormone levels**
[b] **Serum progesterone concentration above 20 nmol/L**

**Source: Applicant Table 10, Summary of Clinical Pharmacology Studies, page 18.**

## Medical Reviewer's Comment

- The Applicant did not do a specific study to determine if the serum LNG concentration during the 3 years of use of Liletta suppressed the hypothalamic-pituitary ovarian axis in women using the IUS. Although this is not an efficacy

issue with IUSs, ovulatory changes can also affect the menstrual cycle and bleeding profile.

### 4.4.3 Pharmacokinetics

The pharmacokinetic (PK) characterization of Liletta is based on data obtained from the sub-studies in the phase 3 L102 clinical study. No stand-alone formal clinical pharmacology studies were submitted to the NDA.

Liletta was designed to have an initial *in vitro* LNG release rate of ~20 µg/day. The *in vivo* release rate is approximately 16.3 µg/day at end of Year 1, 14.3 ug/day at end of Year 2, and is reduced to approximately 12.6 µg/day at end of Year 3. The mean LNG *in vivo* release rate is approximately 15.6 µg/24 hours over the period of three years as estimated by the mean of the initial and 3-year release rates.

**Table 2: LNG Load and Release in 3 IUSs**

| IUS | LNG Load | Initial LNG Release | Interim Data | Later Release |
|---|---|---|---|---|
| **Liletta** | 52 mg | 18.6 ug/day | 16.3 ug @ Year1<br>14.3 ug @ Year 2 | 12.6 ug @ Year 3 |
| **Mirena** | 52 mg | 20 ug/day | NA | 10-14 ug @ Year 5 |
| **Skyla** | 13.5 mg | 12 ug/day | 10 ug @ 1 Month | 5 ug @ Year 3 |

**Source: Reviewer table: data from 3 approved labels.**

**Medical Reviewer's Comments**

- For comparison: Mirena, which is approved for up to 5 years of use, has an initial *in vitro* release rate of 20 µg of LNG daily, declining to a range of 10 to 14 µg per day after five years.
- Skyla, recently approved for up to 3 years of use, was designed to have an initial *in vitro* LNG release rate of 12 µg/day. The *in vivo* release rate is approximately 10 µg/day in Weeks 3 to 4 and is reduced to approximately 5 µg/day after three years. The mean LNG *in vivo* release rate is approximately 6 µg/24 hours over the period of three years.
- The Liletta and Mirena T-frames have the same width and vertical stem (length) of 32 x 32 mm. The Skyla IUS is slightly smaller in dimensions (i.e., 28 x 30 mm).

## 5 Sources of Clinical Design and Review Strategy

### 5.1 List of Studies/Clinical Trials

For determination of efficacy, NDA 206229 consists of a single, large phase 3 study performed entirely in the US.

**Table 3: Clinical Trial L102 for Efficacy Determination**

| Study Number/Protocol location, duration | Design | Study population | Number of women by treatment group | Main outcomes |
|---|---|---|---|---|
| L102<br>-29 sites, US<br><br>-November 2009 to December 2012 for enrollment | -3 year multicenter, open label,<br>2-arm*<br>- 2 year extension for Liletta arm | - Healthy<br>-16 to 45 years<br>-Nulliparous or parous women<br>Inserter used | Age 16-35: 1,600<br>Age 36-45: 151<br>Nullip: 1,011<br>Parous: 740<br>THI (2-hand) - 760<br>SHI (1-hand) - 991 | -Pregnancy rate<br>-Bleeding patterns<br>-Safety |

*The initial design included Mirena as a comparator as required by the European authorities; this arm was stopped after 159 subjects had been enrolled. The Mirena data is not adequate to support any comparative claims and is not discussed in this review.

Source: Medical Reviewer table.

**Medical Reviewer's Comments**

- Study L102 was a large phase 3 contraceptive clinical trial performed exclusively in the US. Inserter THI-001 was used in 760 women from December 2009 to July 2010, with 731 successful insertions. The trial was suspended to redesign the inserter and resumed with the (b) (4) (b) (4) .
- There were 3 sub-studies for women age 16-35 years at selected sites during the L102 study
  - N= 74: *Ex vivo* assessment of Liletta from among those IUSs that were removed or expelled, which were analyzed for residual LNG content
  - N= 40: LNG PK (PK BMI study) in 21 non-obese and 19 obese women through Month 30
  - N= 50: Endometrial thickness in a subgroup of subjects by transvaginal ultrasound evaluations at both baseline and Month 12 visits was evaluated for European Regulatory filing purposes only.
- Based on earlier agreements with Medicines360, the evaluation of Liletta's efficacy will be based on the 12-month and cumulative 3-year adjusted PI for women 16 to 35 years of age from the MITT population of the phase 3 L102 Study. The Year 2 and Year 3 PIs will also be considered.
- Because currently, Liletta approval is sought for 3 years of contraception, the ongoing extension of the phase 3 study for 5 years of IUS use will not be addressed in this review.

There were three additional studies that were submitted to this NDA. Studies (b) (4) and L104 are discussed in detail in Sections 7.4.5.1.1 and 7.4.5.1.2 of this review.

- Levosert-20: a 12-36 month phase 3 supportive menorrhagia trial performed in Eastern Europe; intended to seek approval of a menorrhagia indication in Europe.
- (b) (4)
- Study L104: a phase 1 clinical trial to assess the successful placement of Liletta using the new optimized THI-002 inserter in nulliparous and parous women age 18-45 was carried out following completion of Study L102, when the Applicant determined that the TBM inserter would be a two-handed version because of possible patent issues with the (b) (4) inserter.

**Table 4: Additional Supportive Clinical Studies**

| | Study Name Sites | Study population | Number of women by treatment | Main outcomes |
|---|---|---|---|---|
| **Levosert-20**<br>- 21 sites, Europe | - 12 to 36 months, -<br>multicenter,<br>- open label,<br>- 2-arm<br>- 2 year extension for LNG-IUS arm | - 18 to 45 years<br>- nulliparous & parous women | **Enrolled: 280**<br>for 12 months.<br>2 year extension: 70<br>-Liletta 35<br>-Mirena 35 | - Bleeding patterns/ blood loss<br><br>-Safety |
| (b) (4) | (b) (4) | (b) (4) | (b) (4) | (b) (4) |
| **L104**<br>- 6 sites, USA | - single IUS placement with a **THI-002 inserter**<br>- ultrasound verification | - 18 to 45 years<br>- nulliparous & parous women | **Enrolled: 100**<br>Completed:100<br>-Nullip: 57<br>-Parous: 43 | - insertion analysis<br>- adverse events<br>- pain, bleeding |

**Source: Medical Reviewer table.**

**Medical Reviewer's Comments**

- The supportive Levosert-20 menorrhagia trial is a multi-center, single-blind, randomized, phase 3 study to investigate the IUS efficacy for the treatment of heavy menstrual bleeding. It was conducted at 21 sites in 3 European countries (Serbia [4], Romania [11], and Macedonia [6]) between December 2007 and January 2010.
- (b) (4)
- Study L104 was performed at 6 centers in 100 women (57% nulliparous) to assess the safety and performance of an optimized two-handed inserter, designated as the THI-002 inserter, between February 4 and March 24, 2014.

## 5.2 Review Strategy

The primary phase 3 clinical trial, L102, and the supportive trials listed above were reviewed to assess the safety of Liletta and th (b) (4) inserters. Contraceptive efficacy was assessed based solely on the phase (b) (4) L102 trial. The effectiveness of the THI-002 inserter, which was not utilized in the hase 3 trials, was assessed based on results of Study L104.

## 5.3 Discussion of Individual Studies/Clinical Trials

### 5.3.1 Primary Clinical Trial (Study L102)

5.3.1.1 Study Title

The title of the primary Study L102 is "Phase 3, multi-center, open-label, study of a levonorgestrel-releasing intrauterine system for long-term, reversible contraception."

5.3.1.2 Study Objectives

Primary Objective: was to assess the safety and efficacy of the LNG-IUS (Liletta) in nulliparous and parous women 18 to 35 years of age for up to 3 years. The study will continue for up to 5 years as an extension study.

Secondary Objectives:

- safety, tolerability, bleeding patterns, and continuation rates of Liletta
- return of menses after discontinuation of Liletta
- return to fertility after discontinuation of Liletta
- plasma PK of LNG in a subset of 60 subjects with serial sampling over the duration of use
- plasma LNG levels for all subjects starting with Month 36 to support a decision for extended duration of use beyond Month 60

- changes in endometrial thickness based on transvaginal ultrasonography at 1 year and 5 years
- safety and tolerability of Liletta in women between ages 36 and 45 years
- analysis of IUSs that are removed or expelled during the study

**Medical Reviewer's Comment**

- The primary and secondary objectives were agreed to during the meetings held between the Division and the Applicant.

5.3.1.3 Clinical Trial Design

This trial was a multicenter, randomized, open-label study with the LNG-IUS (Liletta). The trial was conducted at 29 study sites in the US and intended to study up to 5 years use of the system. The current NDA is seeking 3 year approval for the LNG-IUS and the Applicant intends to eventually seek a 5 year approval.

The women in the study were between 16 and 45 years of age, in good general health, and in need of contraception. A total of 2,074 women were screened for participation in the study, leading to a total of 1,910 women who were enrolled [1,600 age 16-35, 151 age 36-45, and 159 in the Mirena group]. See Figure 3 for details. The full analysis cohort was used for all safety analyses, defined as including all women for whom the IUS was inserted or the insertion of an IUS was attempted. A total of 1,751 subjects were randomized to receive the LNG-IUS and the second arm (Mirena arm) was stopped after only 159 subjects had been enrolled because the Applicant realized they had enough comparative data to satisfy the European authorities (EMA) for potential marketing approval.

**Medical Reviewer's Comment**

- The Mirena arm was not required by FDA. The only reason for this comparator arm and the endometrial substudy was to satisfy the EMA requirements for marketing approval.

5.3.1.4 Clinical Trial Sites

The study was conducted at 29 centers in the US. The principal investigator at each center was responsible for the conduct of the study. Only physicians qualified by training and experience to perform the LNG-IUS insertions were used as investigators. The number of women enrolled at the different centers ranged from 186 (Eisenberg at Washington University in St. Louis) to 4 (Sogor at Planned Parenthood of Northeast Ohio).

5.3.1.5 Inclusion Criteria

1. Has signed informed consent.
2. Is between 16 and 45 years (inclusive), in good general health and requesting contraception.

3. Regularly sexually active and in a mutually monogamous relationship of at least 6 months at study entry.
4. Willing to rely on the study IUS as the primary method of contraception.
5. Has regular menstrual cycles (length of cycle 21-35 days) when not using hormones.
6. Is willing to comply with the scheduled visit schedule and assessments, including diary completion requirements.
7. Planned to reside within a reasonable driving distance of a research site (approximately 150 miles) for at least 2 years

5.3.1.6 Exclusion Criteria

Subjects were ineligible for participation in this study if they met any one of the following requirements:

1. Currently pregnant
2. Pregnant within 4 weeks prior to study entry
3. Planning pregnancy within 24 months of study entry
4. Currently breastfeeding
5. History of ectopic pregnancy without a subsequent intrauterine pregnancy
6. History of trophoblastic disease (benign or malignant gestational) without a subsequent non- trophoblastic intrauterine pregnancy
7. Acute pelvic inflammatory disease or a history of pelvic inflammatory disease without subsequent intrauterine pregnancy
8. History of a positive HIV test or having a partner who was known to be HIV positive
9. History of cervical or vaginal infection (unless successfully treated and considered clinically cured for at least 7 days prior to study entry)
10. Postpartum or post-abortion endometritis unless symptoms resolved at least 4 weeks prior to study entry
11. Current persistent, abnormal vaginal bleeding
12. Abnormal Pap test based on the following criteria:
    - Pap test in the 18 months prior to study entry with ASC-US unless:
        - less than 21 years of age;
        - a repeat Pap test at least 6 months later was normal;
        - reflex human papilloma virus (HPV) testing was performed and was negative for high-risk HPV; or
        - a colposcopy (with or without biopsy) found no evidence of dysplasia requiring treatment or treatment was performed and follow-up at least 6 months after the treatment showed no evidence of disease.



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- Pap test in the 18 months prior to study entry with LSIL unless:
  - less than 21 years of age;
  - a colposcopy (with or without biopsy) found no evidence of dysplasia requiring treatment or treatment was performed and follow-up at least 6 months after the treatment showed no evidence of disease.
- Pap test in the 18 months prior to study entry with ASC-H, atypical glandular cells, or HSIL unless colposcopy and/or treatment was performed and follow-up at least 6 months after the colposcopy and/or treatment showed no evidence of disease
- Pap test in the 18 months before study entry with malignant cells
- Pap test more than 18 months before study entry that was abnormal without any appropriate follow-up evaluation

13. History of malignancy of the genital tract (e.g., cervical cancer, ovarian cancer, endometrial cancer)
14. History of breast cancer, or suspicion of breast cancer until proven otherwise
15. History of bicornuate uterus or any other abnormality of the uterus resulting in distortion of the uterine cavity or cervical canal incompatible with placement
16. Known or suspected allergy to LNG or hypersensitivity to any component of the product
17. Bleeding diathesis (inherited or acquired)
18. Use of anticoagulants within 30 days prior to study entry
19. Body habitus or history of lower genital tract abnormalities or prior surgeries which might have prohibited proper visualization of the cervix or not allow the uterus to be appropriately instrumented (Note: any women who met this criterion were to have a pelvic examination prior to enrollment to confirm that the cervix could not be properly visualized for IUS placement)
20. Alcohol or illicit prescription drug abuse at study entry or history of alcohol or illicit or prescription drug abuse within 12 months prior to study entry
21. Use of hormonal contraception for cycle control prior to or at time of study entry
22. DMPA (Depo-Provera®) injection within past 9 months prior to study entry [This exclusionary time period could have been shortened to 6 months if the subject had also had two spontaneous menstrual cycles (required a minimum of 3 menses) that met criteria for normal menstrual cycles]
23. Current use of non-contraceptive estrogen, progesterone, testosterone or other gonadotropins (e.g., hCG)
24. Use of an experimental medication or receipt of an experimental treatment for any condition within 30 days of study entry
25. Study staff or a member of the immediate family of a study staff

26. Any condition or circumstance that, in the opinion of the Investigator, would constitute contraindications to participation in the study or would compromise ability to comply with the study protocol, such as any concurrent medical condition that was not stable and well- controlled, that was likely to worsen, or that may have required recurrent hospitalizations during study participation
27. History of bipolar disorder, schizophrenia, psychosis, major depressive disorder or other major psychiatric disorder according the criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV-TR)

**Medical Reviewer's Comments**

- The above inclusion/exclusion criteria are in accord with standards for IUS insertions, NDA contraceptive clinical trials, and are acceptable.
- There were 6 versions of the study protocol between October 2009 and August 2012 with no major changes in the inclusion and exclusion criteria; women from age 16-45 were included in all the protocol versions.

5.3.1.7 Concomitant Therapy

Concomitant therapy was defined as either the continuation of a treatment started within 7 days (30 days for anticoagulants) of enrollment or addition of a new treatment during the study treatment period.

Excluded Concomitant Therapies while on study treatment included the following:

- Hormonal contraceptives with the following exceptions:
  - An oral, transdermal, vaginal or combined monthly injectable hormonal contraceptive was permitted in the first month only
  - Emergency contraception was to be recommended in any situation when the subject felt the IUS had been expelled and she subsequently had intercourse. Subjects were not discontinued from the study because of emergency contraceptive use
- A previously inserted contraceptive implant or IUS unless the implant or IUS was removed prior to study placement (may have been removed immediately before study IUS placement)
- Any other contraceptive method that could confound the efficacy parameters of this investigational contraceptive was not allowed during study participation. However, if the subject felt the need to protect herself against sexually transmitted infections, she was allowed to use a male condom. If the use of a male condom became a regular part of the subject's contraception, the site Principal Investigator was required to contact the Medical Monitor about the possibility of discontinuing the subject from study participation. All condom usage was documented on the daily subject diaries.
- Any non-contraceptive estrogen, progesterone, testosterone, or gonadotropin (e.g., hCG)

- Misoprostol on day before or day of IUS placement or removal
- Any cervical dilating instrument used during IUS placement other than Pratt dilators, a lacrimal duct probe, or an os finder
- Any investigational treatment or medication other than the LNG20 IUS

Subjects who began to chronically use excluded therapies could be discontinued from the study. Investigators were required to contact the Medical Monitor to discuss possible discontinuation of these subjects.

**Medical Reviewer's Comments**

- All concomitant medications were reported on the CRF as follows: brand name of the medication, start and stop dates, dose, frequency, route of administration and indication.
- The above list is standard and acceptable.

5.3.1.8 Study Procedures

After signed, written informed consent was obtained, screening procedures were performed and eligible subjects enrolled into the trial via an Interactive Voice Response System (IVRS). Enrollment and IUS placement could occur on the same day as the screening procedures. The assigned IUS was inserted by a study investigator using standard sterile procedures for an IUS placement. Additionally, enrollment into the pharmacokinetic (PK BMI) and endometrial thickness ultrasound substudies occurred at the time of IVRS contact and required informed consent for the substudy. The PK study aimed to include as many obese (N= 19) as non-obese women (N= 21) using Liletta.

Scheduled Visits and Phone Calls

For a detailed table of scheduled visits and procedures, see Appendix 9.4, Figure 6 at the end of this review (copied from page 52 of the Applicant's Clinical Study Report). There were 10 scheduled study visits: screening (Visit 1), enrollment (Visit 2), seven interim visits (Visits 3-9 at Months 1, 3, 6, 12, 18, 24, and 30), and Visit 10 at Month 36 after IUS insertion. For women who discontinued early, there was an end of study visit (one month after discontinuing study treatment). A urine pregnancy test was obtained at screening, baseline, at each clinic visit, and at any interim visits if pregnancy was suspected. Telephone assessments occurred at 3 month intervals between scheduled clinic visits, starting at Month 9. The IUS was removed when requested, when clinically indicated, or at the end of 60 months of use.

Routine safety monitoring (AE assessments and vital signs) was conducted for all subjects. An Independent Data Monitoring Committee (IDMC) monitored subject safety throughout study conduct, and was sent reports of all unexpected related SAEs that occurred during the study. The IDMC reviewed all safety data.

Subjects received detailed instructions on how to record vaginal bleeding, dysmenorrhea and other contraceptive use in a daily diary and reported this information during the first 24 months of study participation. Thereafter, only other contraceptive use was recorded on a diary by the subject for the remainder of study participation, in addition to the



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information collected at each study visit. After 24 months, bleeding and dysmenorrhea information was obtained for the remainder of study participation via interviews by study staff during each study contact (every 3 months) during treatment.

Starting with the Month 36 study visit, all subjects in the study had a blood sample obtained at each visit for determination of LNG level. These levels will be utilized to support possible extension of duration of use of Liletta beyond Month 60. In addition, the Sponsor intends to retain all IUSs that are removed or expelled (when available) and analyze an appropriate sample of these for residual LNG levels.

**Medical Reviewer's Comments**

- After discussing the collection of bleeding and dysmenorrhea data with the Applicant, the Division agreed with their plan.
- No formal agreement was made between the Division and Applicant on how to interpret the plasma LNG levels or what criteria to use to allow use of Liletta beyond 60 months.

Screening Visit:
All screening procedures were required to be performed before Enrollment Visit procedures. Although screening test results were not required to be available prior to the Enrollment Visit, all specimens for screening laboratory testing had to have been collected prior to enrollment (IVRS contact). The screening procedures follow here:

- Written informed consent prior to conducting any study specific procedures
- Demographic information
- Medical history, including pregnancy, contraception, menstrual cycles, and vaginal bleeding and cramping patterns
- Medication history for 7 days prior to enrollment (anticoagulant use for 30 days)
- High sensitivity urine pregnancy test (positive test would exclude subject)
- Height, weight, temperature, and blood pressure (all measured at the Screening Visit)
- Breast exam and any clinically indicated physical examination
- Pelvic exam, STD testing and Pap test:
    - Pelvic exam, STD testing and Pap test (if not required for eligibility) could have been deferred to the time of IUS insertion if screening and enrollment visits occurred on the same day and there was otherwise no clinical reason to perform the pelvic examination prior to enrollment
    - Pap test for eligibility:
        - All subjects over 20 years and 6 months old required a Pap test for eligibility from within the last 18 months (see section 6.11)



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        - Enrollment and IUS insertion did not occur until eligibility with a documented test was confirmed
    - Chlamydia testing for all subjects
    - Gonorrhea testing for any subject following a change in sexual partner since last tested or if never tested after change. In addition, HIV and other related sexually transmitted infection testing was recommended
- Hemoglobin, serum creatinine, AST, ALT, and bilirubin
- Review eligibility criteria (subject failing to meet all inclusion/exclusion criteria are to be recorded as Screen Failures)

Enrollment Visit: all subjects were enrolled via the IVRS, given two attempts at the IUS insertion, dispensed the diary and instructions, given instructions for checking the IUS string in the vagina, and scheduled for the next appointment.

Post-insertion Visits: all diaries were collected and reviewed; AEs, concomitant medications and medical history were reviewed. All visits had a high sensitivity urine pregnancy test, and weight and blood pressure were measured.

Treatment Completion/Early Discontinuation Visit: all diaries were collected and reviewed; AEs, concomitant medications and medical history were reviewed. A Complete Bleeding/Cramping Form was completed for early discontinuation after Month 24. Samples for hemoglobin and urine pregnancy were taken; weight, blood pressure, prn sexually transmitted infection (STI) testing, IUS removal, and contraceptive counseling were done.

**Medical Reviewer's Comments**

- The above procedures are standard and acceptable.
- See the Schedule of Study Visits (Figure 6) for details concerning additional hemoglobin and plasma LNG blood samples, breast and pelvic exams, Pap tests, chlamydia testing (done routinely in all subjects 25 years old or younger at Months 12, 24, 36, and 48), and gonorrhea testing.
- The frequency of clinic visits and phone calls between visits is adequate and all subjects were encouraged to call for an urgent study visit if they suspected:
    - Pregnancy
    - IUS expulsion or partial expulsion
    - Pelvic infection
    - Other worrisome symptoms

5.3.1.9 Primary Efficacy Variables

The primary efficacy variable was the number of unintended pregnancies during treatment measured by the Pearl Index (PI) with 2-sided 95% confidence intervals (CI) and life-table analysis (Kaplan-Meier method) in all women age 16-35. A secondary outcome variable was the PI for the women age 36-45.

All efficacy evaluations were conducted on the two patient populations noted below with a subset analysis for the type of inserter used:

- Modified Intent To Treat (MITT): All Liletta subjects between 16 and 35 years of age at study entry for whom the assigned IUS was successfully placed in the uterus and for whom there was at least one report of pregnancy status after inserting the IUS.
  - Cycles in which an additional method of birth control was used were deleted from the number of evaluable cycles used in the calculation for the PI.
- Per Protocol (PP): A subset of the MITT population that excluded subjects with major protocol deviations (identified prior to data lock).

**Medical Reviewer's Comments**

- The Applicant's [redacted] (b) (4) pproval for 3 years of Liletta use.
- In Study L102, a highly sensitive urine pregnancy test was performed at each study visit so that the test result was available before the subject left the study site.
- NDA approval will be based on the MITT PI based on elimination of all cycles that used an additional method of birth control.
  - Pregnancies judged to have occurred while a study IUS was in place and up to and including 7 days after IUS discontinuation (determined by ultrasound and medical assessment) were included in these calculations.
  - PIs were obtained for each individual year of treatment, and cumulatively over the first two years of treatment, and the first three years of treatment.

If the woman became pregnant during the study, she was to contact the study site as soon as possible. The investigator verified the pregnancy by ultrasound or serum HCG testing. Removal of the LNG IUS was then recommended. If the Liletta could not be easily removed, termination of the pregnancy was to be considered. If the woman wished to continue the pregnancy and the IUS could not be removed, she was informed about the risks and the possible consequences of a preterm birth. The course of all pregnancies was then to be monitored.

Pregnancies were to be allocated to the time periods relevant for the calculation of the PIs described above, e.g., a pregnancy that occurred on Day 400 would be relevant for the Year 2 PI, the cumulative two-year PI, and the cumulative three-year PI.

During the study, use of additional contraceptive methods was recorded in the subject's daily diary and queried at each study visit by the investigator. In the event of documented use of an additional method of birth control (e.g., condoms to prevent STI, a diaphragm or spermicide, or any excluded hormonal preparations), the period of additional contraceptive use (in terms of calendar months) was excluded from the exposure time. All subjects were instructed to use condoms for contraception starting at least 7 days before Liletta removal, unless the removal was to take place during the first 7 days of the menses. Therefore, the week before removal of the IUS was subtracted from the exposure for all subjects.

The PI was calculated using 28-day cycles and using 13 such cycles as equal to 1 woman-year of exposure.

**Medical Reviewer's Comment**

- Exposure data was given as woman-years (WY) based on individual exposure in terms of days of treatment. A total of 365 days was equal to one woman-year.

As a secondary analysis, the cumulative pregnancy rates were calculated using the Kaplan-Meier method.

5.3.1.10 Secondary Efficacy Variables

Efficacy analyses for the PI were performed for the following subsets:

- Inserter type used (THI-001 or (b) (4)
- Age group 36-45 years
- Parity (nulliparous or parous)
- Years 1, 2, and 3
- PI with no cycles excluded
- BMI subgroups: < 25.0, 25.0-29.9, 30.0-39.9, ≥ 40
- Race

**Medical Reviewer's Comment**

- No per protocol (PP) population analysis was conducted for the Pearl Index or Life Table analyses because only 3 subjects (< 0.2%) of the 1,545 subjects in the Liletta MITT population had major protocol deviations that could impact the efficacy outcome, and none of them had a pregnancy. I concur with the Applicant's determination that the resulting PP findings would be virtually indistinguishable from the MITT population.

PK Analysis (Subset)

Fifty-seven subjects 16 - 35 years of age participating in the main study were enrolled into the PK BMI substudy: 21 non-obese subjects (BMI < 30) receiving Liletta, 17 non-

obese subjects receiving Mirena, 19 obese (BMI ≥ 30) subjects receiving Liletta. Data from 6 additional subjects were not evaluable and therefore not included in the report submitted with the NDA.

**Medical Reviewer's Comments**

- The above PK BMI substudy report will be reviewed by the clinical pharmacology team. Per protocol, all the Mirena subjects were to be non-obese; the reason for this is unclear.
- The PK profile of LNG, based on data from plasma LNG levels at Months 36, 42, 48, 54 and 60, will be assessed at a future date for all subjects still enrolled in the L102 study at these timelines.

Endometrial Thickness (Subset)

Endometrial thickness was evaluated in 50 subjects aged 16-35 years with data obtained both at Baseline and Month 12. However, due to timing of the study visits there were insufficient samples collected during the secretory (luteal) phase of the menstrual cycle to allow an informative assessment of the difference between pre-placement endometrial thickness compared to post-placement thickness. The mean endometrial thickness at 12 months after placement was 3.8 ± 1.7 mm.

**Medical Reviewer's Comment**

- The Division did not review the protocol for this substudy and did not require the study. The study was done solely as a requirement for the European regulatory authorities.

5.3.1.11 Safety Data

The following safety parameters were monitored during the clinical trial:

- AEs, SAEs presented using System Organ Class (SOC) and Preferred Term (PT)
- Concomitant medications
- The occurrence of dysmenorrhea
- Ease of Liletta insertion and removal rated by the investigator
- Liletta insertion/removal ease and pain rated by the subject
- The IUS expulsion and perforation rates
- The overall discontinuation rates
- Ectopic pregnancies
- The occurrence of pelvic inflammatory disease (PID)
- The occurrence of ovarian cysts (these were reported as AEs if they were abnormal non-functional cysts and/or had a diameter > 3 cm)
- Vital signs



Reference ID: 3706342

- Physical and pelvic examinations, including vaginal and cervical smears and vaginal ultrasound
- Clinical laboratory tests
- Endometrial safety (subset only) at baseline, Months 12 and 60

5.3.1.12 Protocol Amendments

The original protocol M360-L102 (dated October 19, 2009), was amended five times. Clinically significant amendments are listed below. All of the amendments were acceptable to DBRUP and helped to clarify uncertainties in the protocol or reflected changes that became apparent as the clinical trial progressed; details are found on page 35 of the L102 Clinical Study Report (CSR) and are summarized below.

Amendment 1

Amendment 1 dated January 25, 2010 specified the following:

- Modified inclusion/exclusion criteria: non-emancipated subjects had to have parental consent to participate, removed exclusion requirements for low-grade abnormal Pap smears in women under age 21, and deleted exclusion related to previously inserted IUD or IUS.
- Changed the final time point for the PK and BMI substudy from Month 36 to Month 30, and clarified the concomitant medication section.
- Required Chlamydia testing for all subjects ≤ age 25 and added information on monitoring for vaginal infections and abnormal Pap smears.
- Timing of endometrial thickness assessment would be at enrollment, and Months 12 and 60.
- Revised AE definitions and causality.
- Added additional PI and life table pregnancy analyses

Amendment 2

Amendment 2 dated August 11, 2010 specified the following:

- Modified the PK and BMI substudy from 80 to 60 subjects age 16-35 with cohorts < 30 BMI and ≥ 30 by removing 20 obese Mirena subjects from the study; the reason for the protocol change was not given.
- Modified requirements for Pap smear testing by subject age and baseline status
- Added dysmenorrhea as a secondary outcome measure
- Recommended HIV and other STI testing if a subject changed sexual partner
- The timelines for SAE and pregnancy reporting were changed to within 24 hours
- Added stratification by age, parity and BMI for safety and efficacy secondary analysis
- Modified subject diary to allow determination of vaginal bleeding and dysmenorrhea based on changes from baseline, thus eliminating duplicate recording on AE CRF and subject diary



Reference ID: 3706342

- Added provision that pregnancy rate of > 3% was unacceptable and would result in study termination. [Note: because the pregnancy rate was so low, this never became an issue.]

Amendment 3

Amendment 3 dated March 7, 2011 corrected the Schedule of Events (Appendix A).

Amendment 4

Amendment 4 dated January 25, 2012 contained several changes:

- Decreased the anticipated number of enrolled subjects in both arms
- The MITT population is limited to Liletta subjects
- Revised the inclusion/exclusion criteria: subjects must be sexually active, in a monogamous relationship for at least 6 months, and reside within a reasonable distance of study site for at least 2 years. Excluded women with major psychiatric disorders or prescription drug abuse within 12 months of enrollment.
- Pregnancies occurring on treatment are only those occurring with the Liletta in place
- Only 3 methods of cervical dilating instruments allowed; others added to prohibited concomitant treatment
- If needed, a second IUS insertion attempt could occur on a day within 30 days of the subject's signed consent
- Revised the Pap requirements and formal testing procedures
- Added instructions for procedures when a positive pregnancy test occurs while subject is on treatment or at 30-day safety follow-up
- Required ultrasound evaluation to assess pregnancy, missing IUS strings, and possible IUS AEs
- Added appendices providing guidelines on management of pregnancy and IUS issues

Amendment 5

Amendment 5 dated August 10, 2012 added a few additional protocol changes:

- Replaced site diaries with the Bleeding/Cramping Form after Month 24.
- Pregnancies on treatment included those up to or on 7 days after IUS discontinuation.
- All diagnostic ultrasounds should have a permanent image taken and saved.
- Revised analysis of vaginal bleeding patterns to consist of incidence and duration of bleeding.
- Revised Pap test requirements to reflect changes in ASCCP guidelines.

5.3.1.13 Protocol Deviations

The CSR for Study L102 had the following statements:



Reference ID: 3706342

"A total of 2,292 protocol deviations were reported, an average of 1.2 deviations per subject enrolled. The most frequently reported deviations were related to out of window (979) or missed visits (384), representing 59.5% of all deviations. It should be noted that the 108 subjects discontinued classified as lost to follow-up had to miss at least two consecutive study visits or contacts to be considered lost to follow-up; therefore, the lost to follow-up subjects accounted for at least 216 (56.3%) of the missed visits (216/384)."

"A total of 355 laboratory deviations were identified. When required labs were not obtained or results came back as not evaluable, the testing or repeat testing was generally performed at the next study visit, with the exception of an immediate unscheduled visit for STI testing. This included failure to perform gonorrhea/Chlamydia testing in 103 instances when indicated."

"There were a total of 207 consenting deviations, 98 of which were due to failure to obtain consent again after a revised ICF became available."

**Medical Reviewer's Comments**

- The above-noted deviations totaled 1,925 and accounted for 84% of all deviations. Visiting procedure deviations accounted for an additional 12%.
- It is unlikely that the protocol deviations affected the reliability/validity of the study data or final analysis.
- All subjects (Liletta or Mirena) were analyzed according to the actual IUS placed.

### 5.3.2 Supportive Clinical Trial (Levosert-20)

5.3.2.1 Study Title

Study Levosert-20 is entitled: "A multiple center, randomised, parallel group, single-blind clinical trial, to assess the therapeutic equivalence in terms of efficacy and safety of Test product (Levosert) and Reference product (Mirena) in patients with menorrhagia – Phase III (Therapeutic equivalence)"

This supportive phase 3 clinical trial assessed the therapeutic equivalence, in terms of safety and efficacy, of Levosert and Mirena in patients with menorrhagia. The study was conducted by Uteron in Europe for potential European registration. Two hundred-eighty (280) women had either Levosert or Mirena placed (patients were unaware of their treatment group). The THI-001 inserter was used for all patients. The treatment period was 12 months, with a study extension of up to 36 months for a subset of women (N = 70). Safety objectives were to analyze the safety profile of Levosert-20 compared to Mirena with respect to changes in body weight, and hemoglobin and ferritin values. Efficacy was based on the mean variation of the volume of menstrual blood loss determined by a pictographic method. This was not a contraceptive study.

Per agreement with FDA (Type C meeting held June 26, 2012; see response to Question 11), the data from this study was not included in the overall summary of safety or the SAS datasets.

**Medical Reviewer's Comments**

- The 243 page Clinical Study Report was examined as part of this NDA review. The total number of TEAEs was equally distributed between the Levosert (N= 141) and Mirena (N= 139) subjects. There were 5 SAEs in the Levosert group in the first year; all 5 were expected events, 4 were unrelated to treatment and 1 was estimated as possibly related; only one of these subjects was discontinued from the study.
- In the study there were only 3 nulliparous women in the 280 enrollees, so few data are available for nulliparous subjects.
- There were no pregnancies, signs of PID, or perforations in either treatment group.
- The safety data from this menorrhagia study do not raise any safety concerns or new signals

# 6 Review of Efficacy

Efficacy Summary

One phase 3 clinical trial (L102) was submitted to the NDA to support the marketing claim of prevention of pregnancy for up to 3 years. The primary efficacy variable was the number of unintended pregnancies during treatment measured by the PI with 2-sided 95% CI and life-table analysis (Kaplan-Meier method). The PI was based on 28-day equivalent cycles and was defined as the number of pregnancies per 100 woman-years.

Evidence of efficacy of Liletta is based on data from the phase 3 clinical trial L102. Based on the data from this study, in the Liletta 16-35 year old MITT population of 1,545 women, Kate Dwyer, PhD, the FDA's statistical reviewer's, calculated PI rates, excluding cycles in which other birth control methods were used. The PIs were the following: for the principal Year 1- 0.15 (0.02, 0.55), Year 2- 0.41 (0.11, 1.05), and Year 3- 0.00 (0.00, 0.98). These PIs provide evidence to support the efficacy of Liletta in the population targeted for marketing.

**Table 5: FDA Pearl Index by Year and Cumulative, MITT, Study L102**

| | 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 : FDA table by Kate Dwyer, PhD; data up to December 19, 2014.**

**Medical Reviewer's Comments**

- The values calculated by FDA in the above table are virtually the same as the Applicant's, and represent an acceptable level of efficacy.
- The cumulative 5-year pregnancy rate reported in the current product label for Mirena is 0.7 per 100 women.
- The approved label for Skyla states the PI at 1 year is 0.41 (95% upper confidence limit of 0.96) and the 3-year cumulative pregnancy rate was 0.9 per 100 women or 0.9%, with a 95% upper confidence limit of 1.7%.
- Although cross-study comparisons are difficult to make, it appears that the overall contraceptive efficacy for Liletta in women age 16-35 is acceptable and similar to that of the other LNG IUSs, Mirena and Skyla.
- Analysis of all the women in the study shows that Liletta is very effective for up to 3 years in both nulliparous and parous women age 16-45 and at any BMI up to and including morbidly obese women.

## 6.1 Indication

The Applicant's proposed indication for Liletta is the prevention of pregnancy for up to 3 years. Current continuation of the L102 trial will provide data from Years 4 and 5 to support a future efficacy supplement to seek approval of a duration of use up to 5 years.

### 6.1.1 Methods

Primary Analysis

The primary efficacy analysis for the approval of Liletta is based on Study L102.

**Medical Reviewer's Comment**

- By previous agreements made with the Division (Pre-IND meeting held 10 September 2009, Type C meeting held 26 June 2012, and the Pre-NDA meeting held 17 September 2013), the Division required only one phase 3 clinical trial to support an NDA for this product. This is typical of the Division's requirements for hormonal contraceptives. The contraceptive efficacy of Liletta is therefore based on data obtained from the primary Study L102.

The MITT population included all subjects between 16-35 years of age at study entry for whom the assigned IUS was successfully placed in the uterus and for whom there was at least one assessment of pregnancy status after placing the IUS. In Study L102, the primary efficacy evaluation of pregnancy prevention in the MITT population included 1,545 Liletta subjects between the ages of 16 and 35 years (Efficacy Group), inclusive.

Contraceptive efficacy was based on the number of pregnancies that occurred during treatment or for which the estimated date of conception was within 7 days after IUS removal or detection of expulsion. The primary efficacy endpoint was the PI for the MITT population.

Secondary Analysis

In Study L102, the secondary analysis was the cumulative failure rate using the Kaplan-Meier method calculated using total exposure time based on exposure days and based on 28-day cycles. Other secondary analyses were descriptive bleeding data, treatment compliance, and return to fertility.

### 6.1.2 Demographics

Subject demographics and baseline characteristics are summarized for the Liletta MITT efficacy population in Table 6 . By definition, all subjects in the MITT population were between the ages of 16 and 35 years, and included 11 (0.6%) Liletta subjects 16-17 years old. In the Liletta group, 78.6% of subjects were white, 12.9% were African-American and 8.5% other. For ethnicity, 14.6% reported their ethnicity as Hispanic or Latina.

Nulliparous subjects comprised 61.7% (n=1,011) of the Liletta MITT population. Almost one- fourth (24.2%) were defined as overweight (BMI 25-29.9), one-fourth (24.3%) were defined as obese (BMI ≥ 30) and 5.0% morbidly obese (BMI ≥ 40).

**Table 6: Baseline Demographics (MITT Population), Study L102**

| Demographic Data | 16-35 Yr Olds (N=1,545) |
|---|---|
| **Age (years)** | |
| **Mean (SD)** | 26.2 (4.4) |
| **Median** | 26 |
| **Ethnicity [N (%)]** | |
| **Hispanic or Latina** | 226 (14.6) |
| **Race [N (%)]** | |
| **American Indian or Alaska Native** | 19 (1.2) |
| **Asian** | 60 (3.9) |
| **Black or African American** | 199 (12.9) |
| **Native Hawaiian or Other Pacific Islander** | 5 (0.3) |
| **White** | 1,211 (78.6) |
| **Multiple Races Indicated** | 47 (3.0) |
| **BMI ($kg/m^2$)** | |
| **N** | 1542 |
| **Mean(SD)** | 26.8 (6.7) |
| **Median** | 24.8 |
| **Min, Max** | 15.8, 60.4 |
| **BMI 25-29.9 [N (%)]- overweight** | 373 (24.2) |
| **BMI ≥30 [N (%)]- obese** | 374 (24.3) |
| **BMI ≥40 [N (%)]- morbid obesity** | 77 (5.0) |
| **Partner Status [N (%)]** | |
| **Lives with Partner** | 886 (57.3) |
| **Does Not Live With Partner** | 659 (42.7) |
| **Nulliparous [N (%)]** | **954 (61.7)** |

**Source: Sponsor Table 6, L102 Clinical Study Report, pg 95.**

## Medical Reviewer's Comments

- One strength of this large study is that all the clinic sites were in the US, so there is no issue of using data from foreign countries in determining the efficacy of the product in a US population.

- The total number of women in the MITT (1,545) is acceptable and provides adequate exposure for both efficacy and safety data. The total safety population (1,751) includes women up to age 45 and is larger than the MITT population.
- The racial/ethnic mix is representative of the US population of reproductive age women.
- The number and percentage (>53%) of women who are overweight, obese, or morbidly obese is useful as there is great interest in characterizing the effectiveness of hormonal contraception in heavier women. In addition, this group is at higher risk of VTEs when using combination hormonal contraception. An IUS is generally a safer and more effective contraceptive choice for this group.
- The percentage of nulliparous women is also useful. This group of women is often in need of reliable long-term contraception.

Table 7 summarizes demographic characteristics for the Liletta MITT population by inserter type. (b) (4)

**Table 7: Demographics by Inserter Type- MITT Subjects, Study L102**

| | LNG20 16-35 Yr Olds (MITT) | |
|---|---|---|
| | THI-001 Inserter (N=611) | (b) (4) |
| **Age (years)** | | |
| **Mean(SD)** | 26.3 (4.6) | |
| **Median** | 26 | |
| **Ethnicity [N(%)]** | | |
| **Hispanic or Latina** | 108 (17.7) | |
| **Race [N(%)]** | | (b) (4) |
| **American Indian or Alaska Native** | 14 (2.3) | |
| **Asian** | 13 (2.1) | |
| **Black or African American** | 86 (14.1) | |
| **Native Hawaiian or Other Pacific Islander** | 2 (0.3) | |
| **White** | 480 (78.8) | |
| **Multiple Races Indicated** | 14 (2.3) | |
| **BMI (kg/m$^2$)** | | (b) (4) |
| **N** | 609 | |
| **Mean(SD)** | 27.6 (7.1) | |
| **Median** | 25.6 | |
| **Min, Max** | 16.9, 55.9 | |
| **BMI 25-29.9 [N(%)]** | 148 (24.3) | |
| **BMI ≥30 [N(%)]** | 176 (28.9) | |
| **BMI ≥40 [N(%)]** | 37 (6.1) | |
| **Partner Status [N(%)]** | | |
| **Lives with Partner** | 365 (59.7) | |
| **Does Not Live With Partner** | 246 (40.3) | |
| **Nulliparous [N(%)]** | 311 (50.9) | |

*Note:* Mean exposure for THI-001= 26.6 (SD 13.2) months and for (b) (4) months.

**Source: Sponsor Table 7, L102 Clinical Study Report, pg 96.**

**Medical Reviewer's Comment**

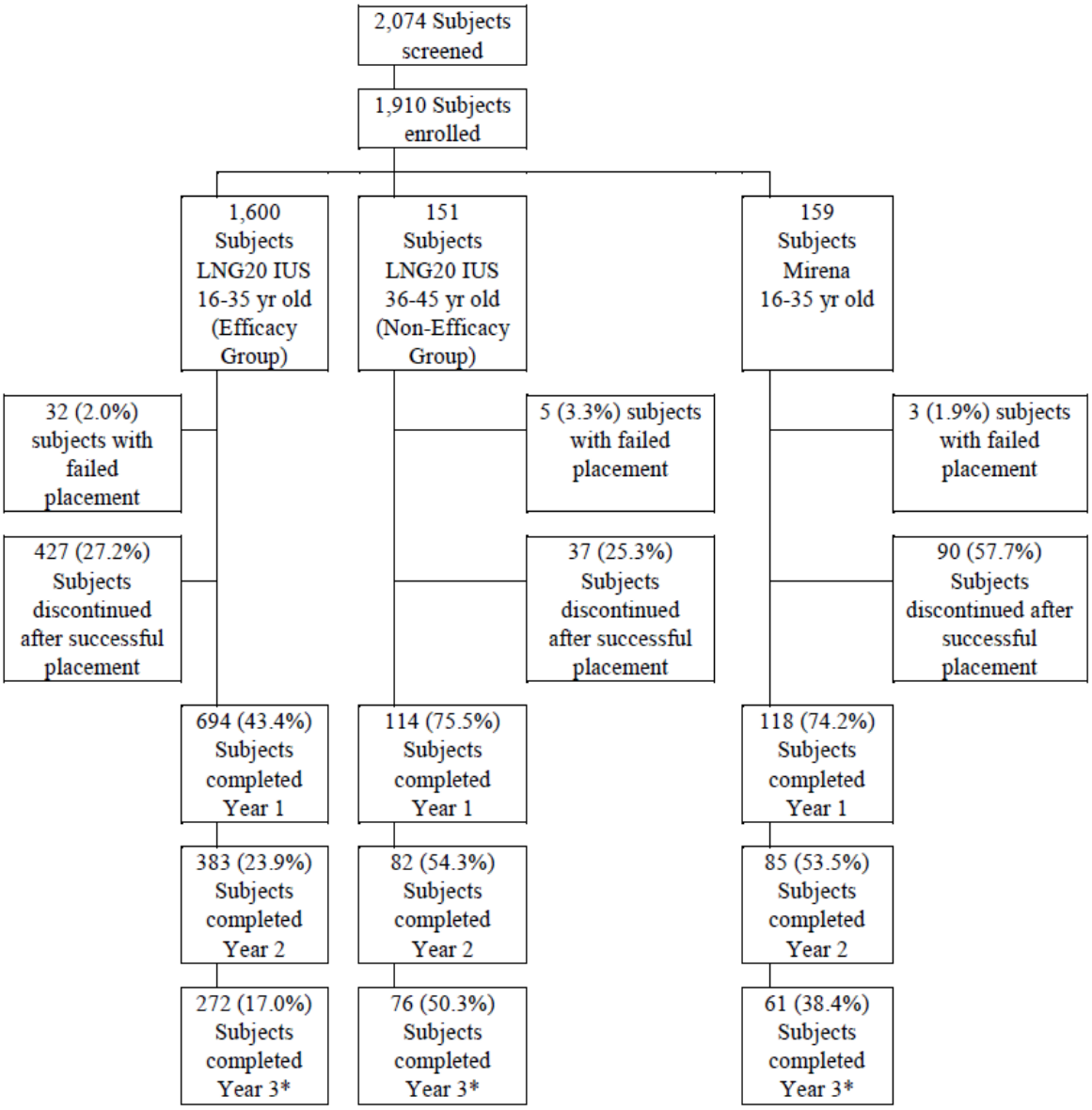
- The differences in demographics are understandable in a clinical trial with 29 clinical centers and the use of two inserters. It is doubtful, however, that the demographic differences are significant. Analysis of the efficacy data for the two inserters is made in Sections 6.1.4.1). In the European menorrhagia study, there were only 3 nulliparous women in the 280 enrollees, so little data is available for nulliparous subjects.

### 6.1.3 Subject Disposition

In Study L102, a total of 2,074 women were screened. Of those screened, 164 women were screen failures and 1,910 were enrolled into the study. Information on screen failures was collected but is not included in the 3-year clinical study report for the ongoing study.

Figure 3 below depicts overall subject disposition for each treatment. Among those screened, 1,910 subjects were enrolled in the study beginning on 28 December 2009, with enrollment completed on 23 April 2013. A total of 1,751 subjects (1,600 Primary Efficacy Group and 151 women age 36-45) had at least one placement attempt with Liletta and 159 (all 16-35 years of age) had at least one placement attempt with Mirena; these subjects constitute the Safety population. The Liletta MITT population, consisting of subjects 16-35 years old who had product use with at least one pregnancy evaluation, includes 1,545 Liletta subjects (Table 6) of which 11 subjects were 16-17 years old.

**Figure 3: Disposition of all Subjects, Study L102**




*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.

**Source: L102 Clinical Study Report, pg 83.**

## Medical Reviewer's Comments

- The numbers and completion percentages above are misleading because all the Mirena subjects have been in the study long enough to complete their maximum of 3 years of IUS placement, whereas most of the Liletta subjects (b) (4) are ongoing and had not completed 3 years of IUS use at the time of the NDA submission data lock.

- The reasons for the 427 women in the Efficacy Group who discontinued after a successful IUS insertion are discussed in Section 7.3.3.

**Table 8: Subject Time in Trial by Inserter, All Subjects, Study L102**

| | THI-001 Inserter | | SHI-001 Inserter** | |
|---|---|---|---|---|
| | Liletta 16-35 Yr Olds N (%) | Liletta 36-45 Yr Olds N (%) | Liletta 16-35 Yr Olds N (%) | Liletta 36-45 Yr Olds N (%) |
| **Safety Population[1]** | 648 (100.0) | 112 (100.0) | 952 (100.0) | 39 (100.0) |
| **MITT Population[2]** | 611 (94.3) | 0 | 934 (98.1) | 0 |
| **PP Population[3]** | 610 (94.1) | 0 | 932 (97.9) | 0 |
| **Endometrial Thickness Population[4]** | 59 (9.1) | 0 | 0 | 0 |
| **PK BMI Population[5]** | 41 (6.3) | 0 | 0 | 0 |
| **Completed (Safety Population)[6]** | | | | |
| **Month 1** | 608 (93.8) | 107 (95.5) | 931 (97.8) | 39 (100.0) |
| **Month 2** | 594 (91.7) | 107 (95.5) | 916 (96.2) | 38 (97.4) |
| **Month 3** | 582 (89.8) | 105 (93.8) | 900 (94.5) | 38 (97.4) |
| **Month 4** | 571 (88.1) | 101 (90.2) | 813 (85.4) | 38 (97.4) |
| **Month 5** | 561 (86.6) | 99 (88.4) | 732 (76.9) | 38 (97.4) |
| **Month 6** | 553 (85.3) | 97 (86.6) | 670 (70.4) | 36 (92.3) |
| **Month 7** | 539 (83.2) | 97 (86.6) | 612 (64.3) | 35 (89.7) |
| **Month 8** | 534 (82.4) | 95 (84.8) | 539 (56.6) | 35 (89.7) |
| **Month 9** | 529 (81.6) | 95 (84.8) | 456 (47.9) | 35 (89.7) |
| **Month 10** | 508 (78.4) | 93 (83.0) | 368 (38.7) | 35 (89.7) |
| **Month 11** | 499 (77.0) | 92 (82.1) | 287 (30.1) | 33 (84.6) |
| **Year 1** | 487 (75.2) | 91 (81.3) | 207 (21.7) | 23 (59.0) |
| **Year 2** | 383 (59.1) | 82 (73.2) | N/A[7] | N/A[7] |
| **Year 3** | 272 (42.0) | 76 (67.9) | N/A[7] | N/A[7] |

****The maximum exposure in this group was 16 months.**

**Note: Denominator for percentages is the number of Safety Population. Months are defined as durations of 30.4 days between IUS placement date and last known date of use.**

**[1]All subjects who had an IUS placement attempt, successful or unsuccessful.**

**[2]Subjects 16-35 years of age with at least one complete 28-day cycle of use or with an on-study pregnancy.**

**[3]Three subjects were excluded from the PP population (1 from THI-001 and (b) (4) The Efficacy Group included only the 16 – 35 age group; therefore, a PP population was not defined for the 36 – 45 age group.**

**[4]Subjects enrolled in the Endometrial Thickness substudy and who have at least one post-placement endometrial thickness measurement.**

**[5]Subjects enrolled in the substudy and have at least one post-placement PK assessment and no major protocol deviations.**

**[6]Based on having duration of use that is equal to or greater than that time point; Year 3(Month 36) visit had a ±14 day window.**

**[7]Mean exposure for THI-001= 26.6 (SD 13.2) months and for (b) (4)**

**Source: L102 Clinical Study Report, Table 3, pg 86.**

Combining the two inserter groups, the product use data from the original NDA submission and Safety Update are shown in the following table.

**Table 9: Duration of Continuous Product Use (All Subjects)**

| | Liletta Age 16-35 years | Liletta Age 36-45 years | Liletta Totals (N= 1,714) | Mirena Age 16-35 years |
|---|---|---|---|---|
| ≥ 1 year | 1286 (82.2%) | 126 (86.3%) | 1,412 (82.4) | 119 (76.3%) |
| > 2 years | 495 (31.6%) | 96 (65.8%) | 591 (34.5) | 85 (54.5%) |
| > 3 years | 307 (19.6%) | 76 (52.1%) | 383 (22.4) | 64 (41.0%) |

**Source: Sponsor Table 9.1, L102 Safety Update (data cutoff 5/30/14).**

**Medical Reviewer's Comments**

- Continuous use data does not equate with discontinuation data, as this is an ongoing clinical study and many subjects who used the [redacted] (b) (4) are still enrolled in the ongoing study.
- Enrollment with all subjects (safety population) for the THI-001 inserter (N = 760) was from December 2009 to July 2010; there was then a 20-month delay before enrollment with the [redacted] (b) (4) was started in March 2012 and completed in April 2013; the cutoff date for the data in the original NDA submission was July 2013.
    - All of the women in the THI-001 group had a potential use of 3 years (July 2010-13).The maximum possible exposure for subjects in the THI-001 group was 44 months (December 2009- July 2013.
    - The maximum possible exposure for any subject for whom the SHI-001 was used would be 16-17 months (March 2012 to July 2013)
    - The mean duration of exposure for the 16-35 year old MITT THI-001 group was 25.8 (SD 13.2) months, [redacted] (b) (4)
- The percentage of subjects age 16-35 completing use of Liletta at Years 1, 2, and 3 is quite low compared to the Mirena and older Liletta groups listed above. This is primarily explained by the early enrollment of all the Mirena subjects and the delay in enrollment of the 991 women (all ages) for [redacted] (b) (4) Another possible explanation is that the younger subjects were more likely to move, withdraw consent, desire pregnancy, or switch to another method of contraception.
- The cumulative exposure (use of Liletta) at 3 completed years is sufficient to make an approval decision for the Applicant's request for 3 years of contraceptive efficacy for their product in women age 16-35 years.
- Additional 3-year data will become available when the [redacted] (b) (4) cohort reaches 3 years of exposure.

6.1.3.1 Reasons for Study Discontinuation:

Among all Liletta-treated subjects, 37 subjects (2.1% of all 1,751 enrolled subjects) discontinued due to a failed IUS placement attempt. Among the 1,714 Liletta subjects with successful placements, the most frequent reasons for discontinuation from the study across the two age groups were AEs (9.4% AEs plus 2.9% expulsions), loss to follow-up (5.0%), and a desire to become pregnant (3.6%). Within the Liletta subjects, no single reason for discontinuation other than AEs and loss to follow-up accounted for more than 3% of subjects who discontinued. Forty-nine (2.9%) of the 1,714 Liletta subjects were discontinued due to partial (1.6%) or complete (1.3%) IUS expulsion. A partial expulsion was defined in the protocol as "visual evidence of the lower portion of the IUS stem protruding through the cervical os or evidence of increased bleeding and/or cramping complaints with the presence of the IUS in the lower uterine segment".

See Table 10 for details.

**Table 10: Subject Discontinuation (All Subjects)**

| | Liletta 16-35 Yr Olds N (%) | Liletta 36-45 Yr Olds N (%) | Total Liletta N (%) | Mirena 16-35 Yr Olds N (%) |
|---|---|---|---|---|
| **Subjects Enrolled** | 1,600 | 151 | 1,751 | 159 |
| **Discontinued After Failed Placement** | 32 (2.0) | 5 (3.3) | 37 (2.1) | 3 (1.9) |
| **Discontinued After Placement**[1] | 427 (27.2) | 37 (25.3) | 464 (27.1) | 90 (57.7) |
| **Reason for IUS Discontinuation**[1] | | | | |
| **Desires Pregnancy** | **60 (3.8)** | **2 (1.4)** | 62 (3.6) | 14 (9.0) |
| **Expulsion of IUS** | 45 (2.9) | 4 (2.7) | 49 (2.9) | 12 (7.7) |
| **Complete** | 17 | 4 | 21 | 5 |
| **Partial** | **28** | **0** | 28 | 7 |
| **Adverse Event**[2] | 145 (9.2) | 16 (11.0) | 161 (9.4) | 20 (12.8) |
| **Investigator Decision** | 10 (0.6) | 1 (0.7) | 11 (0.6) | 0 |
| **IUS No Longer 1° Method of Contraception** | 7 (0.4) | 0 | 7 (0.4) | 0 |
| **Sponsor Decision** | 2 (0.1) | 0 | 2 (0.1) | 0 |
| **Subject Relocation** | 29 (1.8) | 3 (2.1) | 32 (1.9) | 5 (3.2) |
| **Subject Withdrew Consent** | 18 (1.1) | 1 (0.7) | 19 (1.1) | 11 (7.1) |
| **Lost to Follow-Up** | 79 (5.0) | 7 (4.8) | 86 (5.0) | 22 (14.1) |
| **Other** | 32 (2.0) | 3 (2.1) | 35 (2.0) | 6 (3.8) |

**Note: Denominator for percentages is the number of subjects enrolled.**

[1]Only applicable for subjects who have a successful placement and discontinued. Removal of the IUS as a result of an adverse event is included in the adverse event category.

[2] IUS Expulsions not included.

**Source: Sponsor Table 4, L102 Study Report pg 87.**

**Medical Reviewer's Comments**

- Comparing discontinuation rates between Liletta and Mirena is distorted because all the Mirena subjects had completed their 3 year of study time, whereas the 993 subjects that had used the [redacted] (b) (4) inserter were enrolled for a maximum of 16-17 month by the time of the data lock in July 2013.
- The Mirena arm was stopped after only 159 subjects had been enrolled because the Applicant realized they had enough comparative data to satisfy the European authorities (EMA) for potential marketing approval. It is not clear if the sites then encouraged the Mirena subjects to discontinue from the clinical study. Thus, a better comparison for discontinuation rates is with Skyla which was approved by the Division in January 2013.
- The Liletta results were compared with the discontinuation rate for Skyla, a LNG IUS with ~1,400 women using the approved IUS. The listed reasons for discontinuation are slightly different, but the following categories are similar:
    - Failed insertions: Liletta 2.1% vs Skyla 0.4%
    - Consent withdrawal: 1.1% vs Skyla 1.8%
    - Lost to follow up: 5.0% vs 4.4%
    - Expulsion of IUS: 2.9% vs 3.1% [Mirena label states 4.9%]
    - Protocol deviation: 0.7% vs 1.1%
    - Pregnancy: 0.23% vs 0.63%
- The listing for the 35 subjects with "Other" category in the above table was checked and included the following in descending order:
    - Subject request (no reason stated): 18
    - Change to non-hormonal contraception: 7
    - IUS removal medically indicated: 6 (colposcopy, uncertain pregnancy, string not seen, on exclusionary medication)
    - Sterilization planned (1), multiple partners (1), private MD would not care for subject if using an IUS (1), and study visit inconvenience (1)

### 6.1.4 Analysis of Primary Endpoint(s)

6.1.3.2 Study L102

The Applicant's primary pregnancy rate was originally based on data from women 16 to 35 years of age during the first year of use (Year 1 PI) and during the second year (Year 2 PI). After discussions with DBRUP, it was agreed that the Applicant would also calculate the PI for Year 3 and the cumulative 3-year PI. The primary efficacy population included all women in the MITT, which was defined as all randomized women between 16-35 years of age at study entry in whom an IUS was successfully placed in the uterus and for whom there is at least one report of pregnancy status after inserting the IUS.

Contraceptive efficacy was assessed by calculating the PI and performing a Kaplan-Meier life-table analysis based on the number of pregnancies occurring during study treatment or for which the estimated date of conception was within 7 days after Liletta removal or detection of expulsion. Months in which conception did not occur but which included the use of back-up contraception or exclusionary concomitant sex steroids were not included in the calculation of the PI. Per protocol, the analysis at Years 3, 4 and 5 would only be completed if the efficacy of Liletta for the preceding years of use was established. This hierarchical approach would not require adjustment to the acceptable precision required for the confidence interval of the PI.

**Medical Reviewer's Comments**

- The primary outcome measures were agreed to between the Division and the Applicant. The Applicant is seeking approval for 3 years use of the IUS.
- It should be noted that all positive pregnancy tests for the entire study were reviewed, as well as all possible on-treatment pregnancies, and only two on-treatment pregnancies were identified by this reviewer and by the Applicant. The other positive tests were associated with a pregnancy conceived before IUS insertion or more than 7 days after IUS removal.

  The Applicant did initially count those first cycles in which additional contraception was used. The Division asked the Applicant to recalculate the PI values excluding those initial cycles and to include all pregnancies and IUS exposure up to a cutoff date of January 30, 2015.

At the time of the original NDA submission, a total of 2 pregnancies occurred in the MITT population during the first three years after IUS insertion. Both of the pregnancies occurred in the first year of use. One subject had a uterine perforation and displacement of the IUS outside of the uterus. The second subject has an ongoing intrauterine pregnancy as of the cut-off date of 12 July 2013, and the IUS could not be detected in the uterus by ultrasound. A third pregnancy was observed on the L102 study, but this pregnancy occurred after three years of use in this subject. Therefore, this pregnancy is not included in the efficacy calculations up to three years post-insertion in this NDA application.

However, data submitted to the NDA in August 2014 (120-Day Safety Update) found 3 additional pregnancies (two ectopic) and one more ectopic pregnancy was reported in a January 2015 15-day safety report (see details that follow).

There were no pregnancies in the women who were age 36-45 at study enrollment, so the PI point estimate in this age group is zero.

**A summary of each pregnancy follows:**

*Subject 110-0030*. The subject was G4P2Ab2, weighed 151 lbs. (BMI 22.7 kg/m$^2$) and at the time of enrollment was 35 years old. She had the IUS placed with the THI-001 inserter on April 16, 2010 and a TVU on May 14, 2010 showed an intrauterine IUS.



Reference ID: 3706342

This subject had an ongoing issue with the IUS strings not being evident upon physical exam and multiple ultrasound examinations conducted and evaluated by the site investigators were interpreted as demonstrating the study IUS was intrauterine. When the subject was evaluated for her reported pregnancy, the investigator's initial evaluation was that the subject had an intrauterine pregnancy with a spontaneous abortion on (b) (4) [IUS in the cavity, no gestational sac, weakly positive urine pregnancy test]. Plans were made to have the subject return for IUS removal and study withdrawal.

The subject was diagnosed by another physician on (b) (4) with an ectopic pregnancy which required treatment by exploratory laparotomy and right salpingectomy; a pre-op CT scan of the abdomen showed free fluid in the abdomen and the IUS in a transverse lie on the right side of the pelvis. The investigator considered the appropriate diagnosis to be heterotopic pregnancy. Two days after the surgery, the subject underwent another exploratory laparotomy for a complication of the previous surgery during which Liletta was incidentally located in the cul-de-sac protruding through the posterior uterine wall near the internal os level and removed.

The Applicant requested the site ultrasound images taken throughout her participation for independent review by a gynecologic ultrasound expert whose opinion was that none of the images demonstrated intrauterine presence of an IUS. Furthermore, the ultrasound examinations in early pregnancy did not demonstrate an intrauterine pregnancy but, rather, a collection of intrauterine fluid consistent with a pseudosac, which is suggestive of an ectopic pregnancy. It is the Applicant's conclusion that in this case, the IUS perforated through the uterus and was actually present in the peritoneal cavity at the time the pregnancy occurred. Moreover, the Applicant concluded that a rare heterotopic pregnancy did not occur and that this event represented solely an ectopic pregnancy that occurred while the IUS was not in the uterus

**Medical Reviewer's Comment**

- The CRF was reviewed and this reviewer concurs with the Applicant's final opinion on this case. This is counted as an on-treatment pregnancy. It is unclear why the surgeon did not do a better job exploring for the extrauterine IUS during the first exploratory laparotomy as it was easily found with the second laparotomy that was performed 2 days later.

*Subject 103-2033*. The subject was parous, weighed 141 lbs. (BMI 25.0 kg/m$^2$) and at the time of the pregnancy was 28 years old. She had the IUS placed with the (b) (4) inserter on August 31, 2012. Serial β-hCG and transvaginal ultrasounds demonstrated an early intrauterine pregnancy with an estimated date of conception of May 23, 2013. On 5 ultrasound examinations done sequentially after the positive pregnancy test, the IUS was not visible in the uterus. The subject refused an x-ray for diagnosis of a perforation or an IUS expulsion until after delivery. The subject had an estimated date of delivery of 12 February 2014 and delivered a healthy baby at an estimated 38 weeks gestation. There is no additional information about the location of the IUS or if it was believed to be expelled prior to the pregnancy.

The principal investigator Christine Brody, MD stated:

In my opinion as the PI, the pregnancy may represent product failure; I cannot make a definitive conclusion until further testing is performed to confirm whether the IUS was expelled or has undergone trans-uterine migration into the abdominal cavity. It is my opinion that this case likely represents an expulsion which I believe likely occurred on or before (b) (4) Based on the likely date of conception estimated by the transvaginal ultrasound examination findings, I feel this case does not represent an IUS failure. However, until the time that trans-uterine migration is fully excluded (with the concept that a perforated IUS that is still present in the body represents a failure), I cannot reach a definitive conclusion.

**Medical Reviewer's Comment**

- The CRF was reviewed and this reviewer concurs with investigator Brody's opinion on this case. Perforation or IUS expulsion remain unclear, but this is counted as a pregnancy on-treatment by both the Applicant and the Division.

*Subject 125-0005*. A 22 year old parous subject was reported pregnant and is included in the study data base and in the safety section of the Study Report as her date of conception was reported on (b) (4), before the 12 July 2013 data cutoff. This subject was placed with a Liletta using the THI-001 inserter on (b) (4) so the ectopic **pregnancy occurred at 3 years and 3+ months after the IUS insertion**.

She went to the ER with lower abdominal pain, had a positive pregnancy test, and an ultrasound showed a pelvic mass. The IUS was removed vaginally in the ER and the ectopic was initially treated with intramuscular methotrexate with follow up β-hCG testing scheduled. However, she went on to have laparoscopic surgery 13 days after the ER visit. Because this SAE did not occur within the first 3 years, it is not considered an on-treatment pregnancy and therefore is not calculated in the efficacy assessment for the approval of Liletta.

**Medical Reviewer's Comment**

- The CRF was reviewed and this reviewer concurs with the Applicant's final opinion on this case that it occurred during the fourth year of the study and will not be counted as a pregnancy in the MITT Primary Efficacy group for the 3-year approval of Liletta.

**Four additional pregnancies (cutoff date December 19, 2014)**

Subject 101-2098. 32 year old G4P4 female with the IUS for 21 months. She presented with vaginal bleeding and severe lower abdominal pain, positive pregnancy test, and ultrasound findings of a normal IUS placement and a complex left adenexal mass. She was taken to the OR and a laparoscopic left salpingectomy plus suction of the hemoperitoneum performed. The IUS was removed vaginally and she was discharged home following the surgery (without an overnight stay).

Subject 135-2025. 21 year old G0P0 female with the IUS for 17 months. She presented with lower abdominal pain and feeling lightheaded. A pregnancy test was positive (β-hCG 1065) and an ultrasound showed no intrauterine pregnancy but free fluid in the abdomen. The intrauterine IUS was removed, laparoscopy performed with normal fallopian tubes visualized and the right ovary cauterized. Pathology reports showed no chorionic villi on endometrial or ovarian tissue, but chorionic villi identified in the peritoneal blood. She was treated with methotrexate after the surgery. Diagnosis was an extrauterine pregnancy.

Subject 133-2091. 27 year old G0P0 female with the IUS for 21 months. She had a positive home pregnancy test, came to the clinic where a transvaginal ultrasound showed a normal IUS placement and no intrauterine pregnancy. The IUS was removed. A small (8x8x10 mm) right adenexal mass was identified; serial β-hCG values were 925, 875, and 798. She elected to be treated with methotrexate 93 mg IM and was closely followed. No major surgery was needed and the diagnosis was that of a resolving right ectopic pregnancy with a follow up plan of serial hCG testing and repeat methotrexate if indicated.

Subject 130-2019. 34 year old G3P1 female with a BMI of 42.3 conceived when the IUS was in place for 14+ months (Year 2). Urine pregnancy tests were positive and two ultrasounds showed a non-viable intrauterine pregnancy and the IUS in-utero. The IUS was removed easily and intact. At last report, the subject was deciding between expectant versus medical management for the non-viable pregnancy.

**Table 11: Reported On-treatment Pregnancies, MITT, Study L102**

| **Study L102**[1] | **N = 1545** | | | |
|---|---|---|---|---|
| | **Uterine** | **Ectopic** | **Other**[2] | **Total** |
| Year 1 | 1 | 1 | | 2 |
| Year 2 | 1 | 3 | 0 | 4 |
| Year 3 | 0 | 0 | 0 | 0 |
| **Total** | 2 | 4 | 0 | 6 |

**[1] This study did not have any pregnancies with an estimated date of conception within 7 days after the IUS removal.**
**[2] Spontaneous abortions where no intrauterine gestation was documented.**
**Source: Reviewer table based on data up to December 19, 2014.**

**Medical Reviewer's Comments**

- The pregnancy rate is quite low for the first 3 years with this IUS. It will be interesting to see what data comes from the extension of the ongoing study up to 5 years of use.
- As noted, 4 additional pregnancies (3 ectopics and 1 intrauterine pregnancy occurring in Year 2) were reported subsequent to the original data cutoff date. The Applicant recalculated the Pearl Index using the additional pregnancies and exposure data with a cutoff date of December 19, 2014.

Table 12 below lists the FDA-calculated PIs by year and cumulative 3-year index for the MITT population. Exposure data is based on 28-day cycles of individual exposure up to December 19, 2014.

**Table 12: Pearl Index by Year and Cumulative 3-year (MITT Population)**

| | 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 : FDA table by Kate Dwyer, PhD; data up to December 19, 2014.**

**Medical Reviewer's Comments**

- The MITT and unadjusted (no cycles excluded) PIs were almost identical, because there was relatively little use of back-up contraception resulting in non-evaluable cycles.
- These values are very close to those of the Applicant.

**Efficacy by Inserter Type**

During the course of Study L102, two different inserters were used. The study was initiated with a two-handed inserter (THI-001) that was used in 648 subjects in the age 16-35 group. After investigator-reported difficulty in placement, enrollment into L102 was suspended for 20 months, (b) (4)

The distributions of subjects within each inserter type were generally comparable, (b) (4) compared to 28.9% for the THI-001 inserter. Nulliparous subjects (b) (4) of those Liletta subjects with the (b) (4) inserter compared to 50.9% for the THI-001 inserter. For both inserters, the proportion of nulliparous subjects was well above the original Division requirement that the study enroll at least 20% nulliparous subjects.

**Medical Reviewer's Comments**

- (b) (4)
- The to-be-marketed (TBM) THI-002 inserter is generally supported by the 3-year data available with the THI-001 inserter, since the TBM inserter is a modification of THI-001. I would expect any differences due to inserter type would primarily show up in Year 1, with early problems such as expulsions, perforations, etc. There is no clinical reason to think AEs in later years would be much impacted by the inserter used.

**Non-Efficacy Group (age 36-45):**
Because no pregnancies were reported among women age 36-45, the PI point estimate is zero. However, for completeness, Table 13 does highlight the number of 28-day cycles of use for this subgroup at Year 1, Year 2, and Year 3.

**Table 13: PI by Year and Inserter Type- Study L102 Population Age 36-45**

| | THI-001 Inserter[A] N = 107 | | (b) (4) |
|---|---|---|---|
| Cumulative Data Through | Additional BC Cycles Excluded | No Cycles Excluded | |
| | | YEAR 1 | |
| 28-day Cycles | 1,252 | 1,263 | |
| On-treatment Pregnancies | 0 | 0 | |
| Pearl Index (95% CI) | 0.00 (-, 3.82) | 0.00 (-, 3.79) | |
| | | YEAR 2 | |
| 28-day Cycles | 2343 | 2359 | |
| On-treatment Pregnancies | 0 | 0 | |
| Pearl Index | 0.00 (-, 2.05) | 0.00 (-, 2.03) | |
| | | YEAR 3 | |
| 28-day Cycles | 3278 | 3301 | |
| On-treatment Pregnancies | 0 | 0 | |
| Pearl Index | 0.00 (-, 1.46) | 0.00 (-, 1.45) | |

**Source: Modified from Sponsor Table 10.2, L102 Study Repo**

**Medical Reviewer's Comments**

- There were no pregnancies in this older group of women, so the Pearl Index is zero. Although this group is not the primary focus of this review, this method of contraception is an important choice so efficacy data needs to be established. No new pregnancies were reported with the most recent December 19, 2014 cutoff date.
- Further data for efficacy in the older age group are likely to be forthcoming from the Applicant in their report of the full five years of use in the Liletta study.

**Life Table Pregnancy Rates:**

Life table pregnancy rates for the Liletta MITT population with no cycles excluded were very similar to those observed when cycles were excluded for use of other birth control methods. The life table estimates derived for Year 1, Year 2 and Year 3 are shown in Table 14.

**Table 14: Life Table Pregnancy Rates- L102 Study MITT Population**

| | Population | N | Cumulative Pregnancy Rate | 95% Confidence Interval[2] |
|---|---|---|---|---|
| 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, 0.77) |
| Year 3 | ITT - All Subjects | 1,691 | 0.49 | (0.22, 1.10) |
| | MITT - ITT ages 16-35 | 1,545 | 0.55 | (0.24, 0.77) |

**Source: FDA statistician and Applicant's calculations; data to December 19, 2014.**

**Medical Reviewer's Comments**

- For reporting the cumulative pregnancy rate, life table estimates are better than the Pearl Index because these estimates are conditional probabilities over time that accurately incorporates the exposure (high risk and low risk population).
- Both the PI (0.22) and Kaplan-Meier (0.55) calculations are based on data up to December 19, 2014 derived from primary Study L102 support the efficacy of Liletta over the 3-year time period.
- This study included women ages 16 to 45. For final approval and labeling purposes, the PI is usually derived from the enrolled women who are age 35 or less at the time of enrollment, so only the younger MITT cohort is reviewed for the primary efficacy results. This is because fertility is likely to be lower in women > age 35 years.

The Applicant and Cross Discipline Team Leader (CDTL) Lisa Soule, MD, also looked at pregnancy data by subsets in the women age 16-35, by parity, BMI, and race based

on data through December 19, 2014. The results are shown in Table 15**Error! Reference source not found.**.

**Table 15: Cumulative PI 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**

## Medical Reviewer's 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 data. 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.**
- **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 IUS use, without regard to BMI, parity or race.**

### 6.1.5 Analysis of Secondary Endpoints

#### 6.1.5.1 Bleeding

Per protocol, cramping/pain and bleeding data were collected by different methods over the course of the study. For the first 24 months, a daily diary was completed by the subject recording occurrence and severity of any bleeding. Initially, the post-24 month data on cramping/pain and bleeding was collected via a recall diary every three months. This collection required subjects to give a day-by-day account of the bleeding and spotting history over the previous 3 months since their last clinic visit. The Applicant determined that the reliability of subject recall over a 3 month period for day-to-day bleeding and spotting was minimal, so in Amendment 5 to the protocol (dated 10 August 2012), the collection of these data was changed to a summary questionnaire completed through subject interview every 3 months.

Prior to implementation of protocol amendment 5, approximately 400 subjects completed the recall daily diary for at least one visit post-24 months in the study. These data are included in the datasets provided with the L102 clinical study report.

Cramping/pain and bleeding TEAEs during the first 24 months were recorded on the subject daily diaries when the subject indicated that her cramping/pain or bleeding was worse than her own subjective baseline. TEAEs were entered into the Adverse Events CRF only when the cramping/pain or bleeding led to IUS discontinuation, qualified as a SAE, or was unrelated to the IUS or IUS procedure.

Amenorrhea

Bleeding occurred more frequently just after IUS placement and then diminished such that a number of subjects became amenorrheic by the end of one year of use and this number continued to increase through 3 years of use. Diary-reported bleeding and/or spotting was assessed by 90-day intervals. The proportion of subjects reporting no bleeding and/or spotting during the initial 90-day interval was 0.6%, increased to 13.6% during Months 4-6, was 19.3% at the end of Year 1 (Interval 4) and 26.4% at the end of Year 2 (Interval 8). At Year 3, using the 3-month summary data, 38% of subjects reported no bleeding and/or spotting over the three months leading up to the Month 36 evaluation. All information though Month 24 was obtained from the subject's daily diary used for the first 24 months. Information for Month 36 was obtained from the summary questionnaires that were completed through the subject interview every 3 months.

**Table 16: Amenorrhea by 90-Day Intervals**

| | Liletta 16-35 Yr Olds (N=1,554) | Liletta 36-45 Yr Olds (N=146) | Liletta Total (N=1,700) |
|---|---|---|---|
| 90-Day Interval 1: | (n=1,554) | (n=146) | (n=1,700) |
| No Bleeding and/or Spotting | 9 (0.6%) | 1 (0.7%) | 10 (0.6%) |
| 90-Day Interval 2: | (n=1,451) | (n=143) | (n=1,594) |
| No Bleeding and/or Spotting | 201 (13.9%) | 16 (11.2%) | 217 (13.6%) |
| 90-Day Interval 4: | (n=875) | (n=128) | (n=1,003) |
| No Bleeding and/or Spotting | 174 (19.9%) | 20 (15.6%) | 194 (19.3%) |
| 90-Day Interval 8: | (n=382) | (n=80) | (n=462) |
| No Bleeding and/or Spotting | 98 (25.7%) | 24 (30.0%) | 122 (26.4%) |
| Interval 12- Month 36 | (n=262) | (n=72) | (n=334) |
| No Bleeding and/or Spotting | 99 (37.8%) | 28 (38.9%) | 127 (38.0%) |

**Source: Applicant Table 68, L102 CSR, page 178.**

### 6.1.5.2 Return to Menses and Fertility after Removal

Subjects who discontinued from the trial and who were not pregnant and did not start a hormonal contraceptive after discontinuation from Study L102 were followed to assess the return of menses after IUS removal, as shown in Table 17. Of the 183 Liletta subjects evaluated, 173 (94.5%) had menses within 2 months of Liletta discontinuation and 180 (98.4%) reported menses within 3 months of Liletta discontinuation.

**Table 17: Return to Menses Post-IUS Removal (L102 Safety Population)**

| | Age 16-35 N = 163 | Age 36-45 N = 17 | All Ages N = 180 |
|---|---|---|---|



Reference ID: 3706342

| | | | |
|---|---|---|---|
| Month 1 | 115 (69.3%) | 10 (58.8%) | 125 (68.3%) |
| Month 2 | 41 (24.7) | 7 (41.2) | 48 (26.2) |
| Month 3 | 7 (4.2) | 0 | 7 (3.8) |
| Cumulative | 98.2% | 100% | 98.3% |

**Source: Modified from Summary of Clinical Efficacy page 16.**

**Medical Reviewer's Comments**

- These data support the expectation of a rapid return to menses following discontinuation of Liletta.
- Of the 3 subjects treated with Liletta who did not have a return of menses in the first 3 months after IUS removal:
  - one had become pregnant at Day 29 post discontinuation
  - one withdrew consent so that no follow-up could be performed
  - the third subject did not have a work-up as indicated by the protocol
- The 120-Day Safety Update showed very small changes in the above table. Revised data for return to menses are 71.8% at Month 1, 22.8% during Month 2, 2.8% during Month 3, and 99.2% (250/252) at the end of Year 1.

Subjects who discontinued from the trial and desired pregnancy (N = 42) were followed for up to 12 months to assess fertility after Liletta removal (see Table 18). Pregnancy was reported in 35 (83.3%) of the subjects within 12 months of Liletta discontinuation, 30 (71.4%) of which occurred within 6 months and 17 (40.5%) occurred within 3 months. None of the pregnancies occurred within 7 days of IUS discontinuation. Two of these subjects were in the over-35 age cohort, and became pregnant at 5 months and 10 months post-discontinuation, respectively. These results complement those observed for return to menses in that subjects seeking to become pregnant do so relatively soon after discontinuing Liletta.

**Table 18: Return to Fertility Post-IUS Removal (L102 Safety Population)**

| | Age 16-35 N (%) | Age 36-45 N (%) | All Ages N (%) |
|---|---|---|---|
| Month 1 | 4 (11.8) | | 4 (11.1) |
| Month 2 | 9 (26.5) | | 9 (25.0) |
| Month 3 | 4 (11.8) | | 4 (11.1) |
| Month 4 | 5 (14.7) | | 5 (13.9) |
| Month 5 | 5 (14.7) | 1 (50.0) | 6 (16.7) |
| Month 6 | 2 (5.9) | | 2 (5.6) |
| Month 7 | 0 | | 0 |
| Month 8 | 1 (2.9) | | 1 (2.8) |
| Month 9 | 1 (2.9) | | 1 (2.8) |
| Month 10 | 1 (2.9) | 1 (50.0) | 2 (5.6) |
| Month 11 | 1 (2.9) | 0 | 1 (2.8) |
| Month 12 | 0 | 0 | 0 |
| PREGNANCIES | 33 (97%) | 2 | 35 (83.3) |
| Not Pregnant by Month 12 | 1 | 6 | 7 (16.7) |
| Totals | 34 | 8 | 42 |

**Source: Modified from original Summary of Clinical Efficacy page 17.**

**Medical Reviewer's Comments**

- These data support the expectation of quick return to fertility following discontinuation of Liletta. Of all the subjects who discontinued from the trial and desired pregnancy, 40.5% were pregnant within the first 3 months after IUS removal and 71.4% (30/42) within the first 6 months.
- The 120-Day Safety Update showed small changes in the percentages of women become pregnant post-IUS removal over time, with 86.8% (59/68) of women evaluated reporting pregnancy within 1 year of Liletta removal. Return to fertility showed little difference between nulliparous and parous women.
    - For nulliparous subjects, 82% (23/28) were pregnant within a year; of these 23 women, 10 were pregnant by Month 3 and 19 by Month 6.
    - For parous subjects, 90% (36/40) were pregnant within a year; of these 36 women 19 (47.5%) were pregnant by Month 3 and 29 (72.5%) by Month 6.

### 6.1.6 Other Endpoints

A PK analysis set was defined for the women in subset 3 in each clinical trial with valid data for PK analysis.

**Medical Reviewer's Comment**

- See the Clinical Pharmacology review regarding the PK data based on plasma LNG levels drawn at specified times in Study L102.

### 6.1.7 Subpopulations

Subpopulations such as parity, age, BMI, and inserter type used are discussed in Sections 6.1.4.1 of this review.

### 6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The Applicant is currently seeking approval of only one dose of LNG for the IUS. Study L102 is ongoing to provide 5-year data on the efficacy of Liletta to support a future increase in the labeled duration of use.

### 6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The data out to three years of use demonstrates that efficacy persists while Liletta is in use. Data for return to fertility are shown in Table 18.

### 6.1.10 Additional Efficacy Issues/Analyses

No additional efficacy issues/analyses were presented.

## 7 Review of Safety

Safety Summary

The safety profile of Liletta did not raise any specific concerns. The bulk of the Liletta safety database consists of the phase 3 Study L102. All women who were enrolled and had an insertion attempt were included in the safety analysis. A total of 1,751 women, including 1,412 exposed for one year and 383 who completed the 3-year study, provided 21,553 28-day cycles (1,658 women-years) of use data up to May 30, 2014 for the Liletta safety cohort. The population was generally healthy, 16 to 45-year old females requesting contraception and predominately Caucasian (78%). The mean (SD) duration of treatment in the total Liletta population was 23.4 months (14.3) while the median was 20.3 months (maximum was 53 months). The study is ongoing for a maximum duration of use of 5 years.

The most common adverse reactions (ARs) reported in the clinical trials included bleeding pattern alterations, vaginal bacterial and yeast infections, headaches, anxiety/depression, pelvic/abdominal pain and discomfort, and acne. Other drug-related AEs were similar to those that are known to occur with the use of Mirena and Skyla and included IUS expulsions, vaginal discharge, ovarian cysts, breast symptoms, and dysmenorrhea. The frequency of SAEs was low. The most common ARs causing discontinuation of study drug were vaginal hemorrhage, device expulsion, and acne.



Reference ID: 3706342

The frequencies of the IUS-related and other significant AEs did not raise any major safety concerns. A total of 4 ectopic pregnancies occurred during the first 3 years of use with Liletta, resulting in an overall rate of 0.23 %. Two ectopics occurred in nulliparous women and 2 in parous women. There were no significant safety problems found in the nulliparous subjects. There were no relevant effects observed with regard to laboratory tests (CBC, chemistry profile, and Pap smears), vital signs, and other safety parameters measured.

In summary, Liletta was demonstrated to be safe in women 16-45 years of age for the proposed 3 year duration of use.

## 7.1 Methods

Subjects with both successful and unsuccessful insertions were included in the safety evaluation for Study L102. By agreement with the Applicant, there was no pooled analysis, although safety data from the 3 supportive studies has been evaluated. The safety population includes all women from the L102 trial, with the other studies being supportive of the overall safety profile. Standard methods of safety analysis are used by the Applicant.

The Applicant is not relying on the FDA's findings of safety and efficacy for other FDA-approved products (e.g., Mirena and Skyla), but safety data from the literature are provided for completeness in demonstrating the overall safety profile of LNG-containing IUSs. The NDA also presents clinical studies published in the scientific literature that have tested the safety and efficacy of LNG products for the purpose of long-term, reversible contraception. A search of PubMed was conducted with very specific (and often multi-term) search criteria as the number of published papers resulting from simple search terms such as "levonorgestrel" or "IUD" or "IUS" was very high. Given the extensive clinical experience with LNG-only products in humans, the Applicant chose to discuss a selection of important and relevant publications to provide a broad overview of the safety profile rather than summarizing the overwhelming body of literature available.

**Medical Reviewer's Comment**

- The methods listed above are acceptable and were agreed to with the Applicant.

### 7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The most important safety data are from the large phase 3 Study L102, which enrolled 1,751 women between the ages of 16-45 to use Liletta, while supportive studies are:

- Study Levosert-20, the menorrhagia trial in 280 Eastern European women to investigate the efficacy of Levosert (LNG-IUS) for the treatment of heavy menstrual bleeding.
- (b) (4)

- Study L104 in 100 US women (57% nulliparous) to assess the safety and performance of an optimized THI inserter, designated as the THI-102 inserter, which was not utilized in Study L102.

### 7.1.2 Categorization of Adverse Events

All SAEs and common AEs were reported using the System Organ Class (SOC) and Preferred Term categories. AEs were also summarized by age category, parity, race, BMI subgroups, and inserter type. Diary-reported cramping/pain and vaginal bleeding and/or spotting were recorded and summarized separately. AEs were also judged by severity [mild, moderate, severe, life-threatening] and relatedness to the use of the LNG-IUS [not related, unlikely related, probably, and related].

### 7.1.3 Pooling of Data Across Studies/Clinical Trials

By agreement between the Applicant and the Division, pooling of safety data was not done because there was only one large phase 3 US study for this NDA submission. The European Study for a menorrhagia indication was supportive and will be discussed later in the review.

## 7.2 Adequacy of Safety Assessments

### 7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

In Study L102, there were two inserters and two different lots for the IUD. Table 19 shows the breakdown for the total enrolled population.

**Table 19: L102 Enrollment by Inserter**

| Time Frame | Liletta Inserter | Liletta Lot | No. Subjects |
|---|---|---|---|
| Protocol Version 1-4 | THI-001 | CT-09A01 | 760 (43.4%) |
| Protocol Version 5-6 | (b) (4) | CT11I09 | 991 (56.6%) |
| Total Enrolled | -- | -- | 1751 |

**Source: L102 Clinical Study Report pg 5.**

**Medical Reviewer's Comments**

- The overall long-term safety data covers 1,600 subjects age 16-35 and 151 subjects age 36-45.
- This review will focus separately on the safety using the two inserters in Study L102 and separately on the findings in (b) (4) and L104. Because the inserter is removed, discarded and has no further contact with the subject once

the IUS was successfully inserted, there is no physiological or other reason that the long-term safety profile should differ according to which inserter was used.

### 7.2.2 Explorations for Dose Response

One dose of LNG was studied in the clinical studies submitted with the NDA. Approval is currently being sought only for Liletta, to be inserted using the THI-002 inserter, and for three years of pregnancy prevention.

### 7.2.3 Special Animal and/or In Vitro Testing

No specific animal and/or *in vitro* testing was indicated or required for this application.

### 7.2.4 Routine Clinical Testing

Routine clinical testing, which included gynecological examinations, Pap smears, safety labs (chemistry, hematology and urinalysis), and pregnancy testing was adequate.

### 7.2.5 Metabolic, Clearance, and Interaction Workup

Not applicable for this submission.

### 7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Routine evaluations for AEs possibly related to progestin IUSs were performed.

## 7.3 Major Safety Results

### 7.3.1 Deaths

One death occurred during the study period up to December 19, 2014. Subject 108-2191 was a 30 year old woman enrolled into the Liletta study using the (b) (4) inserter. She had a history of mild depression and anxiety for approximately 10 years for which she was taking bupropion and clonazepam for the year previous to study enrollment. She was also using clindamycin gel for bacterial vaginosis and Differin gel (adapalene) for acne vulgaris. She was seen for her Month 1 follow-up visit one day prior to the event and did not report any complaints or changes in medication. She committed suicide the next day; the police investigation determined it a suicide. Her boyfriend reported she had attempted suicide ~10 years ago, but this was not disclosed to the study staff during screening. In the Investigator's opinion this was unlikely related to the IUS.

**Medical Reviewer's Comment**

- I agree with the investigator's opinion that the death was not likely related to the IUS that had been in place for only 29 days. As noted, she had a long history of

mild depression and anxiety, and had been on two medications specifically for her condition in the year prior to enrollment.

### 7.3.2 Nonfatal Serious Adverse Events

A summary of the SAEs determined by the Applicant in the original NDA submission for Study L102 are shown in Table 20 below in alphabetical order by SOC. In total, 38 subjects reported 1 or more SAEs with a distribution of 34 (2.1%) subjects in the age 16-35 group and 4 (2.7%) in the older Liletta group. SOCs with the highest incidence of SAEs across all treatment groups were psychiatric disorders (10 subjects), infections (7 subjects) and GI disorders (5); the investigators did not judge any of these as related to the IUS or IUS placement. Ectopic pregnancy was reported in 2 Liletta 16 – 35 year old subjects, as was PID. Five SAEs resulted in discontinuation from the clinical trial; 3 were related to the IUS and expected events.

**Table 20: Treatment-Emergent SAEs (Liletta Safety Population)**

| SOC/Preferred Term | Liletta (N= 1,751) N (%) | SAE Events* |
|---|---|---|
| **Subjects with 1 or more SAE** | **38 (2.2)** | **60** |
| **Congenital, familial**- hamartoma | 1 (0.1) | 1 |
| **GI disorders** | 5 (0.3) | |
| Crohn's- 115-0021 had 12 hospitalizations | 1 (0.1) | 8 |
| Diarrhea | 1 | 1 |
| Enteritis | 2 | 2 |
| Pancreatitis | 1 | 1 |
| Small bowel obstruction | 1 | 1 |
| **Hepatobiliary disorders** | 4 (0.2) | |
| Bile duct obstruction | 1 (0.1) | 1 |
| Cholecystitis acute- GB removed | 1 | 1 |
| Cholelithiasis | 1 | 1 |
| Portal vein thrombosis- hamartoma subject | 1 | 1 |
| **Infections** | 7 (0.4) | |
| Cellulitis- upper ® arm | 1 (0.1) | 1 |
| Clostridial infection- above Crohn's subject | 1 | 1 |
| PID | 2 (0.1) | 2 |
| Pneumonia- pancreatitis subject | 1 | 1 |
| Respiratory tract infection- Crohn's subject | 1 | 1 |
| Tooth abscess | 1 | 1 |
| **Injuries/trauma-** wrist lacerations, 2 MV accidents, pelvic fracture (ATV accident) | 4 (0.2) | 4 |

| SOC/Preferred Term | Liletta (N= 1,751) N (%) | SAE Events* |
|---|---|---|
| **Metabolic**- hyperkalemia | 1 | 1 |
| **Neoplasms** | 4 (0.2) | 5 |
| Fibrosarcoma | 1 | 1 |
| Hemangioma- spleen | 1 | 1 |
| Lipoma | 1 | 1 |
| Malignant melanoma- stage IV | 1 | 1 |
| Thyroid cancer- metastatic papillary | 1 | 1 |
| **Nervous system disorder** | | |
| Ischemic stroke | 1 | 1 |
| Syncope | 1 | 1 |
| **Pregnancy** | | |
| Ectopic pregnancy | 2 (0.1) | 2 |
| **Psychiatric** | 10 (0.6) | 12 |
| Affective disorder | 1 | 1 |
| Alcohol withdrawal- pancreatitis subject | 1 | 1 |
| Bipolar disorder/mania | 4 | 5 |
| Drug abuse | 2 | 3 |
| Suicide (1 attempt; 1 complete) | 2 | 2 |
| **Renal** | | |
| Lithiasis | 1 | 1 |
| Vasculitis-nephrotic syndrome | 1 | 1 |
| **Reproductive system** | | |
| Ovarian cyst | 1 | 1 |
| Vaginal laceration | 1 | 1 |
| **Surgical-** renal transplant | 1 | 1 |
| **Vascular-** DVT- above Crohn's subject | 1 | 1 |

*** 38 Liletta subjects had a total of 60 SAEs.**

**Source: Reviewer table modified from Applicant's SAE Table 47, pg 77, original NDA Summary-Clinical-Safety.**

## Medical Reviewer's Comments

- The only death in the above 38 subjects was a suicide (Subject 108-2191). Clearly women with significant medical conditions that contradict the use of combination hormonal contraceptives can be candidates for a LNG-IUS for contraception. Therefore, some women with renal disease, GI conditions, neoplasms, etc. were enrolled in the clinical trial, and these women account for some of the more unusual SAEs observed in this trial.

- Three of the SAEs (2 ectopics, I ovarian cyst) were considered by the Applicant as drug-related SAEs (thereby called SARs: serious adverse reactions).
- The 5 SAEs listed above that resulted in trial discontinuation were the following:
  - Subject 101-0039: ovarian cyst
  - Subject 125-0005: ectopic pregnancy in Year 4
  - Subject 105-2055: worsening bipolar disorder
  - Subject 110-0030: ectopic pregnancy
  - Subject 113-0004: Stage 4 melanoma
- There were 5, not 4, serious injury/trauma cases: 1 wrist laceration, 1 motor vehicle (MV) accident, 1 pedestrian/MV accident, 1 bicycle/MV accident, and 1 all-terrain vehicle (ATV) accident. None, however, were related to the IUS.

**Applicant's Life-threatening SAEs**

Per protocol (page 61 of 95, Version 6.0), "Life-threatening" means that the subject was at immediate risk of death from the event as it occurred. This does not include an event that might have led to death, if it had occurred with greater severity." Eleven life-threatening events were reported by the Applicant in 9 Liletta subjects. One of the 11 events (ectopic pregnancy) was classified as treatment-related; the remaining events were considered not related to Liletta. All 9 subjects were in 16-35 year cohort, 4 were nulliparous and 5 parous. The Applicant's listing of the 9 subjects included the following; only Subject 110-0030 with the ectopic pregnancy and perforation was judged by the Applicant as definitely treatment-related:

- Subject 110-0030: 36 year old G4P2 had a failed insertion attempt on March 24, 2010 with a perforation due to the sound so the IUS was not inserted. The perforation was evaluated at the local ER and no evidence of complications due to the perforation was found. She was sent home, continued her oral contraceptive, and the IUS was inserted successfully on April 16 at the study site. An ultrasound 4 weeks later confirmed the IUS in the uterine cavity. On December 15, 2010 the strings were not visible, a urine pregnancy test was positive and an ultrasound showed an intrauterine pregnancy (IUP). Heavy bleeding occurred and a repeat ultrasound on December 20 showed an IUP with no gestational sac. A return visit for IUS removal was scheduled.

  On (b) (4) she experienced abdominal pain and vaginal bleeding, went to her local hospital in the Houston area where she had a positive pregnancy test, CT scan showing fluid in the abdomen, and ultrasound findings of a right adenexal mass and probable ectopic IUS. Exploratory abdominal surgery was performed with a right salpingectomy and evacuation of the hemoperitoneum for a ruptured ectopic pregnancy. The IUS was not seen at the time of surgery.

  On (b) (4) she was taken back to the OR because of abdominal pain and a drop in her hemoglobin. The IUS was found in the cul-de-sac protruding through the posterior uterine wall near the internal os level and removed without problems. She was discharged home on (b) (4)

**Medical Reviewer's Comment on Subject 110-0030**

The site was a Planned Parenthood clinic in Houston, TX under the medical director Paul Fine, MD. Her surgical care was at a local hospital and it is not clear who was the surgeon for her operations and care. There are several findings that are difficult to explain given the reported information. 1) The ultrasound at 4 weeks confirmed an IUS in the uterine cavity. 2) The ultrasounds on (b) (4) showed an IUP and missed the location of the IUS. 3) Why the surgeon did not make a better effort to locate the IUS in the OR on (b) (4). 4) On (b) (4), the location of the IUS through the uterine wall at the level of the internal os given the previous CT scan, 2 ultrasounds, and exploratory abdominal surgery. 5) The discharge home so soon after two exploratory laparotomies. In any case, the subject survived the complications.

- Subject 101-0063: 27 year old on chronic peritoneal dialysis had (b) (4) hospitalizations for worsening renal vasculitis, glomerulonephritis and hyperkalemia requiring a renal transplant. Liletta was in place for 18 months.
- Subject 105-2055: 33 year old had the IUS insertion in November 2012; bipolar disorder was diagnosed in (b) (4) and on (b) (4) she experienced a worsening of her disorder. A urine drug screen was positive for opiates, marijuana and benzodiazepines, lithium level was low; she was hospitalized for 9 days and then discharged. The IUS was removed 13 June 2013 "for non-safety reasons" and she was discontinued from the study.
- Subject 123-0005: 22 year old P2 female with a history of hypertension, depression, drug abuse, and intermittent migraines was assaulted by her boyfriend and struck her head on the ground. She was taken to the hospital by ambulance with right-sided facial neuro findings. The next day she was transferred to another hospital for continued care. CT scan and MRI showed soft tissue injury and acute left middle cerebral artery infarct without hemorrhage. An embolic etiology was examined and ruled out. The event of ischemic stroke on study day (b) (4) was considered resolved with sequelae as the effects of the stroke were ongoing.
- Subject 127-0071: 28 year old female with a history of bipolar disorder, attention deficit disorder, multiple suicide attempts, migraines, alcohol and marijuana abuse, attempted suicide during Month 5 with an overdose on Klonopin following a fight with her boyfriend. At the time she was taking 5 different medications for the listed medical conditions. She was admitted to a psychiatric hospital for 4 days and discharged in a stable condition after her psychiatric medications were adjusted. Her IUS was not removed and she continued in the study.
- Subject 128-0048: experienced traumatic liver injury due to a bicycle-motor vehicle accident (the subject was the bicycle rider) on study day 2. The event resolved.

- Subject 133-0004: was diagnosed with stage IV melanoma which was first reported on study day (b) (4). The IUS was removed for non-safety reasons on study day (b) (4) due to this event.
- Subject 141-2071: experienced bilateral lacerated wrists due to physical assault from her estranged husband on study day (b) (4) The event was considered resolved (b) (4) days later.
- Subject 108-2191: 30 year old who committed suicide on study day (b) (4) (discussed as the only death in Study L102).

**Medical Reviewer's Comments**

- The above SAEs as determined by the Applicant were classified as Treatment-emergent (TE) in Table 20 or life-threatening.
- The Applicant states that only one of the life-threatening events, the ectopic pregnancy in Subject 110-0030, was classified as serious and treatment-related. **I consider the following to represent SARs, outlined in Table 21 below.**

**Table 21: Medical Reviewer Serious Adverse Reactions (SARs)**

| Event | Number | Outcome | Comment |
|---|---|---|---|
| Ectopic Pregnancy | 5 | Surgical Rx- 4<br>Methotrexate- 1 | Subject 110-0030* also had an IUS perforation |
| Perforation* | 2 | Surgically removed | Ectopic subject and one other |
| PID/endometritis | 3 | No serious sequelae | Two subjects were hospitalized |
| Ovarian Cyst | 2 | One surgery for 8.5 cm and 2.8 cm bilateral cysts | IUS removal 2 months post-op |
| **Uncertain SAR Category** | | | |
| DVT- **Crohn's subject** | 1 | Treated medically | See Comment below |
| Depression* | ?? | Hospitalizations | See Comment below |

**Source: Medical Reviewer table.**

**Medical Reviewer's Comments**

- It is clear that ectopic pregnancy, perforations, PID/endometritis, and ovarian cysts are potentially SARs because they are definitely or likely related to the IUS. Most ovarian cysts are not serious and resolve with time, but some do not and require surgery and then become an SAR. The same is true of pelvic infections when an IUS is in place.

- Of the 10 reported cases of pelvic infection, all were treated with antibiotics, but the IUS was removed in only 3 subjects. It is difficult to judge which infection cases were "serious"; I judged 3 in this category serious and related to the IUS.
- Expulsions are a significant AE, clearly IUS-related, but do not meet regulatory criteria to be considered an SAE. An unplanned pregnancy is obviously a possible outcome. None of the cases of partial expulsion required surgery.
- Subject 115-0021 had a long history of complicated Crohn's disease and was hospitalized 12 times during the course of the study. She was on multiple medications (8 up to 20) throughout the study and had a past history of superficial venous thrombosis in one leg, and "a blood clot in the leg treated as a deep vein thrombosis due to the proximity to the femoral vein". A documented DVT occurred when the IUS was in place for 24 months. I do not believe the DVT was related to the LNG-IUS in this woman.
- Depression and anxiety were recorded in 16% of the subjects in Study L102. It is debatable whether the LNG in the IUS can cause or worsen depression or psychiatric symptoms. All the women who were hospitalized for psychiatric reasons during this study had previous histories of psychiatric problems and were on active (usually multiple) medication treatment. For that reason, I did not include any of these women as having an SAR, although several had an SAE.

**Reviewer's additional SAE events:**

In my opinion there were several more subjects that should have been listed according to the Applicant's per protocol definition of life-threatening or SAEs. None were fatal and representative cases are listed below. Most of these events are not related to the IUS unless otherwise noted.

- Subject 101-0039: 32 year old with symptomatic ultrasound documented ovarian cysts (right 8.5 cm; left 2.8 cm) on Day 233 after study entry; outpatient laparoscopic ovarian cystectomy was done and she was discharged home the same day. IUS was in place 7+ months; two months later (Day 295) the IUS was removed "in order to prevent possible future ovarian cysts." This reviewer and the Applicant consider this event to be related to the IUS and therefore an SAR.
- Subject 101-0041: 31 year old recovering methamphetamine addict with a large right sulcus vaginal laceration due to a sexual assault; taken to the OR for a surgical repair, received 7 units of packed red cells, and went home on Day 2. The IUS was in place for 45 days; a follow up ultrasound verified correct IUS location.
- Subject 111-2034: 24 year old with a history of depression and anxiety currently treated with an SSRI (Celexa) was admitted to a psychiatric facility with prolonged depression and bipolar disorder. After 6 days she was stabilized and discharged with a diagnosis of bipolar disorder. The investigator and Applicant considered this event unlikely related to the IUS. The IUS was in place for 6 months and she continued in the clinical trial.

- Subject 103-0018: 33 year old with IUS in place for 3 months had a dermatofibrosarcoma on the right lower back requiring wide local excision.
- Subject 103-2034: 27 year old with a bile duct obstruction due to a gallstone that passed spontaneously during a 4-day hospital stay; IUS in place for 5 months.
- Subject 101-0015: 39 year old with cholelithiasis and cholecystitis; had laparoscopic surgery and went home the next day. The IUS was in place for 13 months.
- Subject 107-2004: 25 year old with a history of small bowel obstruction and surgery in 2008 was admitted for a partial bowel obstruction not related to the IUS; with conservative management she was sent home on Day 3. The IUS was in place for 9 months.
- Subject 105-0014: 45 year old with multiple medical conditions (gastric bypass, hypothyroidism, depression, ulcers, migraines, PTSD) on multiple medications was hospitalized with chest pain and severe anxiety. An extensive workup was negative for a cardiac origin and pulmonary embolus; final diagnosis was probable costochondritis and GI reflux. The IUS was in place for 5 months.
- Subject 105-0027: 33 year old with a history of hypertension, panic attacks, depression, migraines, myalgias, and insomnia had worsening chest pain and was admitted to the hospital. At the time of the hospital admission, she was on more than six different daily prescription medications for her medical conditions. An extensive workup was negative and she was sent home the next day. The IUS had been in place for only 3 weeks. Both the investigator and Applicant assessed the hospitalization as not related to the insertion or IUS.

### 7.3.3 Dropouts and/or Discontinuations

In the original NDA data for the Liletta Safety Population of 1,751 subjects, a total of 464 of subjects (27.1%) discontinued from the study after a successful Liletta insertion. Of the 1,751, 12.3% (215) subjects discontinued treatment due to an AE. Of this 12.3%, 2.8% (49 subjects) were due to IUS expulsion: 28 in the THI-001 inserter group and 21 in the SHI-001 inserter group. Of the remaining 9.5% of the population that discontinued due to AEs, no AE accounted for more than 1% of subjects (see Table 22). The most common of these AEs causing discontinuation of the subject were acne (0.9%), menometrorrhagia (0.8%) mood swings (0.7%), dysmenorrhea (0.6%) and uterine spasm (0.6%).

**Table 22: Adverse Events (> 0.5%) Causing Discontinuation by Study Drug**

| AE causing study drug discontinuation (alphabetical order) | Liletta N = 1,751 (% of N) | Mirena (Age 16-35) N = 159 (% of N) |
|---|---|---|
| **System Organ Class/Preferred Term** | | |
| **Acne** | 16 (0.9%) | 33 (1.9%) |
| **Alopecia** | 2 (0.1) | |
| **Depression** | 3 (0.2) | 3 (0.2%) |
| **Dysfunction uterine bleeding** | 3 (0.2) | |
| **Dysmenorrhea** | 10 (0.6) | 13 (0.8%) |
| **Dyspareunia** | 6 (0.3) | |
| **IUS expelled** | 49 (2.8) | |
| **Menometrorrhagia** | 14 (0.8) | |
| **Mood swings** | 12 (0.7) | |
| **Pelvic pain/discomfort** | 6(0.3) | 39 (2.3%) |
| **Uterine spasm** | 11 (0.6) | |

**Source: L102 CSR, Table 45, Page 152. Original NDA data.**

**Medical Reviewer's Comments**

- The above table lists 132 subjects; overall there were 215 subjects who discontinued due to an AE, so 83 subjects with infrequent AEs (<0.5%) are not listed in the above table. Overall, the pattern of 12.3 % of subjects with AEs that led to study drug discontinuation was comparable between 1) the Liletta and Mirena arms, and 2) between the different Liletta treatment groups [by age, parity, and by inserter type].
- In the recent Skyla primary clinical trial, 21.6% discontinued due to an AE and 0.9% discontinued due to an SAE, for a total of 22.5%. The total of 12.3% in the Liletta study is smaller. The reasons for this difference are not clear but probably not significant.
- Combining all types of bleeding/menstrual events (e.g., dysfunctional uterine bleeding, metrorrhagia, menstruation irregular, etc.), 3.6% of Liletta subjects experienced this group of adverse reactions. However, the number of subjects discontinuing due to these bleeding/menstrual symptoms was 1.8%.
    - The bleeding events comprising the 1.8% total here occurred at a rate of 1.0% in nulliparous and 3.5 % in parous women.

Some of the additional reasons for subject discontinuation include lost to follow up (86 subjects, 5.0% of 1,751), a desire for pregnancy (62 subjects, 3.6% of 1,751), "Other" (35 subjects, 2.0%), subject relocation (32 subjects, 1.9%), withdrew consent (19



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subjects, 1.1%), and investigator/sponsor decision (13 subjects, 0.7%). See Table 10 for the list of all 464 discontinuations.

**Medical Reviewer's Comments**

- It is reassuring that the lost to follow up rates for Liletta and Skyla are very similar (5.0 and 4.4%) and low compared to many contraceptive clinical trials that have much higher rates.
- Concerning the "Other" category for subject discontinuation, in Subject Disposition Appendix 16.2 (68 pages) in the Study L102 CSR, every subject is listed. There were 40 subjects, not 35, who had "Other" as the reason for IUS discontinuation. Most common in this category were the following:
  - Subject request - 18
  - Desire to try non-hormonal birth control - 6
  - Request to remove the IUS (no reason stated) - 4
  - No further need for birth control - 3
  - The remaining 9 subjects gave 7 different reasons for IUS discontinuation

### 7.3.4 Significant Adverse Events

#### 7.3.4.1 Pregnancy and Perinatal Conditions

Within the MedDRA SOC of pregnancy conditions, there were 4 ectopic pregnancies in the 16-35 age group with Liletta and none in the 36-45 Liletta age group or in the Mirena cohort.

Ectopic Pregnancies

There were a total of 6 pregnancies reported in the Liletta subjects in the ongoing L102 trial. Of these 6 pregnancies, 4 (67% of all pregnancies) were ectopic.

**Medical Reviewer's Comments**

- As discussed earlier, in the MITT cohort during the first 3 years of Liletta use, there were 4 ectopic pregnancies in a total of 6 pregnancies.
- If a pregnancy occurs with an IUD in place, it is more likely to be an ectopic pregnancy. The 67% rate of ectopic pregnancy (as a percent of all pregnancies) in the Liletta subjects is not surprising for an IUD. The Mirena label states that up to half of pregnancies that occur with Mirena in place are ectopic. For the approved Skyla IUS, 4 of 12 (33%) pregnancies were ectopic.
- Historical prospective data from randomized controlled trials describe a low absolute risk of ectopic pregnancy, which is also reflected in the data for Liletta from the large L102 clinical trial submitted to this NDA, which demonstrates a 0.23% ectopic pregnancy occurrence (4/1751) over 3 years of use. This equated to an incidence rate of 0.13/woman-year of exposure based on the updated total 3,010 woman-years of exposure to Liletta. Per the Mirena label, the incidence of



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ectopic pregnancy in clinical trials that excluded women with risk factors for ectopic pregnancy was approximately 0.1% per year.

7.3.4.2 Infections

Pelvic Inflammatory Disease (PID) and Endometritis

Overall, intrauterine infection was described in 10 (0.6%) Liletta subjects. In 7 cases the investigator classified the infection as "pelvic inflammatory disease" (PID) and in the other 3 subjects infections were classified as "endometritis." All of the subjects who developed PID were in age 16-35 group, with 5 subjects having the IUS placement with the THI-001 inserter and 2 with the SHI-001 inserter (102-2059, 108-2072). Women with PID included 2 nulliparous and 5 parous subjects. Early onset of PID occurred in 2 of the 7 subjects; 1 on the day of placement (102-2059, SHI-001 inserter) and the other on Day 6 (108-2072, SHI-001 inserter). The other 5 cases had delayed onsets: 7.0 months, 8.2 months, 9.6 months, 10.2 months, and 13.3 months following IUS insertion.

PID was classified as serious in 2 of the subjects (115-0041 and 120-0002, both with the THI-001 inserter group), although neither was classified as treatment-related by the investigator because of the later occurrences. Both of the "serious" cases were treated successfully and neither led to the IUS being removed.

Endometritis was reported in 3 (0.2%) Liletta users in the age 16-35 group, all of whom were considered non-serious cases. Two cases, 1 in a parous subject (127-0049) and 1 in a nulliparous subject (127-0033), started on the day of placement. One parous subject (103-0005) had onset on Day 39. All 3 were considered probably related to the placement procedure. The IUS was removed in 1 subject as a result of the event.

All women diagnosed with intrauterine infection were treated with antibiotics with resolution of the infection. The IUS was removed in 3 of the 10 subjects as a result of the events: 2 PID and 1 endometritis.

**Medical Reviewer's Comments**

- The occurrence of PID/endometritis with Liletta (10/1,751 = 0.57%) is similar to the incidence with Skyla (13/3,370 = 0.39%) and Mirena (0.4%).
- Most of the infection cases (9/10) occurred in the first year after IUS insertion, with 4 of the 10 cases within the first week.
- Infection was more frequent in parous (7) than nulliparous (3) women.

Reproductive System and Breast Disorders

The most common (reported in 2% or more in any treatment group) reproductive system and breast disorders are presented by preferred term below. The frequency was very low in all treatment groups.

Ovarian Cysts

Ovarian cysts were reported as AEs in 2.7% of Liletta subjects. There were 22 (2.2%) in nulliparous and 25 (3.4%) in parous subjects. Only 5 (0.3%) subjects discontinued IUS use because of an ovarian cyst. Per protocol and because ovarian cysts occur commonly in reproductive age women, the clinical trial only collected data on women who were symptomatic. Routine ultrasound evaluations for asymptomatic and clinically non-significant ovarian cysts were not performed. Studies of women using Mirena demonstrate that most ovarian cysts found on routine ultrasound scanning are asymptomatic and clinically non-significant.

**Medical Reviewer's Comments**

- In the large comparative Skyla clinical trials, ultrasounds were done more routinely and the overall frequency of all ovarian cysts (including hemorrhagic, ruptured, and torsed) was 13.2% with Skyla and 20.1% with the larger, higher dose LNG IUS also being studied, and 25% with Mirena. The much lower 2.7% incidence for Liletta is only for symptomatic ovarian cysts, so the overall frequency of ovarian cysts is not known.
- In the Skyla study, 0.47% of the subjects (N = 3,625) discontinued the study because of an ovarian cyst, which comparable to the Liletta 0.3% finding.
- Clinical trial data and the medical literature support the notion that as the daily amount of LNG released from the IUS is increased, the incidence of ovarian cysts also increases.

### 7.3.5 Submission-Specific Primary Safety Concerns

Expulsions

Total expulsion was confirmed if the IUS was observed in the vagina or was not visualized in the uterine cavity by ultrasound, or if the woman confirmed that the IUS had been expelled. Partial expulsion was diagnosed if the IUS could be seen in the cervical canal, as confirmed by gynecological examination or by ultrasound. If the IUS was partially expelled it was removed. With either total or partial expulsion, the woman was discontinued from the clinical trial.

**Table 23: Number of Subjects with Expulsions- Study L102**

| Number of Subjects | Liletta Age 16-35 N=1600 | Liletta Age 36-45 N= 151 | Mirena Age 16-35 N=159 |
|---|---|---|---|
| **Expulsions through Month 6** | | | |
| Number in Study | 1,559 | 145 | 155 |
| Number (%) Continuing | 1,422 (91.2) | 132 (91.0) | 130 (83.9) |
| Number (%) Expulsions | 24 (1.5) | 2 (1.4) | 8 (5.2) |
| | | | |
| **Expulsions Months 7-12** | | | |
| Number (%) Continuing | 1,113 (91.7) | 124 (93.9) | 117 (90.0) |
| Number (%) Expulsions | 16 (1.3) | 1 (0.8) | 0 |
| | | | |
| **Expulsions during Year 2** | | | |
| | | | |
| Number (%) Continuing | 574 (84.0) | 104 (92.0) | 84 (71.8) |
| Number (%) Expulsions | 3 (0.3) | 1 (0.9) | 4 (3.4) |
| | | | |
| **Expulsions during Year 3** | | | |
| Number (%) Continuing | 303 (81.0) | 75 (92.6) | 66 (78.6) |
| Number (%) Expulsions | 2 (0.5) | 0 | 0 |
| | | | |
| TOTAL EXPULSIONS | 45 (2.8%) | 4 (2.8%) | 12 (7.7%) |

**Note: Interval data are not cumulative.**
**Source: L102 CSR, Table 72, page 184.**

## Medical Reviewer's Comments

- The majority of the expulsions (53%) occurred within 6 months post insertion; 35% occurred in the next 6 months, totaling 88% of Liletta expulsions that occurred in the first year after insertion. Ten expulsions (20% of the total) occurred less than 30 days after placement.
- When examining expulsions by parity, 14 (1.4%) were in nulliparous subjects and 35 (4.7%) in parous subjects.
- Of the 49 expulsions, 28 (3.7%) were in the THI-001 inserter group and 21 (2.1%) in the (b) (4) group.

  Note: the revised rate is 3.4% based on 10 additional cases reported in the 120-Day Safety Update. This is similar to the rate of 4.9% reported in the Mirena label and 3.2% in the Skyla label. It is important to note that at the time of the

original data cutoff for this Application, subjects in whom inserter SHI-001 was used for placement had not reached 2 years of use; therefore, comparisons of THI-001 and (b) (4) data can only be reasonably made for the first year after IUS insertion. In this reviewer's opinion, unless an expulsion occurs soon after insertion, it is unlikely that the expulsion is related to the insertion device.

Perforation

Three (0.2%) Liletta subjects had a perforation, all in the age 16-35 group and with the THI-001 inserter. One of these perforations, however, was due to sounding prior to IUS placement (Subject 125-0046) and not associated with the inserter. The subject had a successful second IUS placement attempt 25 days later with the THI-001 inserter without any complications and remained active in the study without any IUS-related AEs. This meant that an actual IUS perforation due to the IUS occurred in only 2 (0.11%) subjects.

**Medical Reviewer's Comments**

- Subject 101-0014: a parous woman reported to the clinic for her Month 3 visit without any complaints, but the IUS strings were not visualized and an ultrasound examination failed to show the IUS in the uterus. An abdominal x-ray performed 2 days later demonstrated the IUS was in the abdomen. Laparoscopic removal of the IUS was performed without complications.
- Subject 110-0030: a parous woman experienced an ectopic pregnancy at study day (b) (4) which was treated surgically with salpingectomy via laparotomy. The IUS, which had perforated into the lower pelvic cul de sac was removed during a second laparotomy, performed for evacuation of an intra-abdominal hematoma 2 days following the first operative procedure. See Section 7.3.2 Life-threatening SAEs for further details and reviewer comments.
- The Liletta perforation experience does not appear to vary from that observed with other LNG IUSs.
- There is an increased risk of perforation in lactating women, during the postpartum period, following a second trimester abortion, and with a fixed retroverted uterus. The approved label should note these risk factors.
    - Lactating women and women who were pregnant within 4 weeks of study enrollment were excluded from enrollment in the clinical study.

IUS Insertion Success

Overall Liletta IUS insertion was successful in 97.9% of the 1,751 subjects, with successful placement on the first attempt in 93.9%. Of this total, 96.2% (731/760) had a successful placement with the THI-001 inserter (90.9% for the first placement attempt) and 99.2% (983/991) had a successful placement with the (b) (4) See **Table 24** that follows.

**Table 24: Number of Successful Insertions, Study L102**

| Number of Subjects | Liletta- THI-001 N = 760 n (%) | (b) (4) | Mirena N = 159 n (%) |
|---|---|---|---|
| First insertion attempted | 760 (100%) | | 159 |
| First IUS insertion completed | 689 (90.9) | | 149 (93.7) |
| First IUS insertion not completed | 71 (9.1) | | 10 |
| Second insertion attempted | 48 | | 7 |
| Second IUS insertion completed | 42 (87.5) | | 7 (100) |
| Second IUS insertion not completed | 6 (12.5) | | 0 |
| Total D/C after failed attempt(s) | 29 (3.8) | | 3 (1.9) |
| Overall Success | 731 (96.2%) | | 156 (98.1%) |

**Source: L102 CSR, Table 56, page 163.**

There were 113 failed placement attempts with the Liletta, 6.1% (106/1,751) of first attempts and 9.0% (7/78) of second attempts. The Applicant's analysis [Table 57 of L102 CSR] is summarized by this reviewer for the 106 failed first placement attempts for Liletta based on the reasons provided by the inserting clinician on the IUS Insertion Questionnaire:

- Cervix too tight for IUS insertion in 46 subjects
- IUS caught in the instrument tube in 16 subjects (8 with each inserter type)
- Procedure terminated with sounding in 13 subjects
- String did not release in 8 subjects
- IUS malposition in 5 subjects and came out with string cutting in 4 subjects
- Anatomical issues in 3 subjects and investigator error in 3 subjects
- Sounding less than 5.5 cm in 2 subjects
- Prior IUS unable to be removed in 2 subjects
- Consent withdrawal (2), immediate expulsion (1), and slider issue (1)

**Medical Reviewer's Comments**

- Because of this number of failed or difficult insertions, the Applicant decided to modify the IUS inserter during the Study L102, in order to "optimize the insertion

procedure" by reducing the number of steps required prior to the actual insertion. The insertion procedure per protocol using the modified inserter was unchanged.

- The most frequent reason for a failed first attempt was inability to sound the uterus in 46 subjects. Thirty (65%) of these subjects were nulliparous.
- Discontinuation from the trial after the first attempt occurred in 30 subjects (30/106 = 28.3%) and in 7 subjects (9%) after the second attempt.
    - This small percentage of 2.1% (37/1,751) of the total enrolled subjects is acceptable given the large number of nulliparous subjects in the study.

IUS Insertion Ease

Combined across both inserters, placement was classified by the Investigator as difficult in 11.6% of first attempts and 32.9% of second attempts. For the first attempt in nulliparous subjects, placement was rated difficult in 24% of subjects with the THI-001 inserter and 9.2% with the SHI-001 inserter; difficult placements percentages in parous subjects were 11.4% for the THI-001 and 3.7% for the SHI-001 group. Table 25 shows the ease/difficulty of placement by parity and inserter type for all the 1,751 first attempts in Study L102.

**Table 25: IUS Insertion Ease by Parity and Inserter Type- Study L102**

| Placement Ease | THI-001 | (b) (4) |
|---|---|---|
| | Nullip (N= 348) n (% of N) | Parous (N=412) n (% of N) |
| Easy | 152 (45.1%) | 286 (71.1%) |
| Neutral | 104 (30.9) | 70 (17.4) |
| Difficult | 81 (24.0) | 46 (11.4) |

**Source: Modified by Reviewer from L102 CSR, Table 61, page 168.**

**Medical Reviewer's Comments**

- Clearly there was a difference in the investigator ease of insertion classification for the two inserters, with the (b) (4) inserter leading to easier insertions.
- As noted before, because of the number of failed or difficult insertions with the THI-001 inserter, the Applicant decided to modify the IUS inserter during the Study L102, in order to "optimize the insertion procedure" by reducing the number of steps required prior to the actual insertion. Hence, the study delay and the switch to the (b) (4) 1 inserter.
- See Sections 7.4.5.1.1 and 7.4.5.1.2 for further detailed analysis of the inserter studies (b) (4) and L104 (THI-102).

IUD Insertion Anesthesia

Per protocol, cervical anesthesia could be used at the discretion of the Investigator, either prophylactically or out of clinical necessity in response to procedural pain or discomfort (e.g., tenaculum placement, sounding, placement into cervical canal), and could be topical or intracervical.

Of subjects who had cervical anesthesia, it was indicated by the investigator to have been used for prophylaxis in 87% of all subjects and out of clinical necessity in 13% of subjects. Data for use of cervical anesthesia by parity and inserter type is shown in the Table 26.

**Table 26: Cervical Anesthesia by Parity and Inserter Type- Study L102**

| Local Used | THI-001 | (b) (4) |
|---|---|---|
| | Nullip (N= 348) | Parous (N=412) |
| Yes | 144 (41.6%) | 73 (17.8%) |
| No | 202 (58.4) | 337 (82.2) |

**Source: Modified by Reviewer from L102 CSR, Table 61, page 168.**

**Medical Reviewer's Comment**

- Clearly, cervical anesthesia was more frequent in nulliparous women and used as prophylaxis in the majority (87%) of all cases.

Ultrasound Guidance

Overall, ultrasound guidance was infrequently used during first attempts (4.7%); in 73 (4.6%) of 16-35 year olds and 9 (6.0%) of 36-45 year olds. Per protocol, abdominal ultrasound guidance could be utilized to assist IUS placement, and was generally used only after beginning the placement procedure and the Investigator determining this guidance would be of benefit. Ultrasound guidance use increased to 20.5% of second attempts, which would be expected to be more difficult and require more frequent use of adjunctive measures.

Cervical Dilatation

Per protocol, if after starting the procedure the cervical canal and internal cervical os could not be traversed, the Investigator could perform rigid dilation to facilitate the passage of the inserter. The rate of rigid cervical dilation was 15.6% in first attempts and increased to 37.2% among subjects undergoing a second placement attempt. Rigid dilation was more frequently required when the THI-001 inserter was used with cervical dilation rates during the first and second attempts of 20.6% and 43.8%, compared to rates of 11.8% and 26.7%, respectively, (b) (4). Use of

rigid cervical dilatation for the first insertion attempt is shown by parity and inserter type in Table 27.

**Table 27: Cervical Dilation by Parity and Inserter Type - Study L102**

| Rigid Dilatation | THI-001 | (b) (4) |
|---|---|---|
| | Nullip (N= 348) | Parous (N=412) |
| Yes | 99 (28.6%) | 57 (13.9%) |
| No | 247 (71.4%) | 353 (86.1%) |

**Source: Modified from L102 CSR, Table 61, page 168.**

**Medical Reviewer's Comment**

- It is difficult to interpret the approximate doubling of dilatation rates for both nulliparous and parous women when using the THI-001 inserter compared to the (b) (4) All subjects needed to be sounded first; if this was successful, then usually the IUS inserter would also be successful without cervical dilatation. It appears that the THI-100 inserter was too flexible and tended to kink; in this case further dilatation beyond sounding may have been needed to facilitate the insertion of the THI-100 inserter. In any case, the dilatation rate was a factor in the decision to switch to the (b) (4) inserter later in the clinical trial.

Bleeding with IUS placement

Table 28 below shows the amount of bleeding recorded with the Liletta IUS placement by inserter type and parity for all 1,751 women in Study L102.

**Table 28: Bleeding with Placement by Parity and Inserter Type - Study L102**

| Bleeding | THI-001 | (b) (4) |
|---|---|---|
| | Nullip (N= 348) n (% of N) | Parous (N=412) n (% of N) |
| None | 104 (34.7%) | 152 (41.2%) |
| Spotting | 114 (38.0) | 132 (35.8) |
| Light | 65 (21.7) | 68 (18.4) |
| Moderate | 17 (5.7) | 15 (4.1) |
| Heavy | 0 | 2 (0.5) |

**Source: Modified from L102 CSR, Table 61, page 168.**

**Medical Reviewer's Comments**

- There is very little difference in each bleeding category when comparing the two inserters by parity (nulliparous vs parous).
- Heavy bleeding was recorded in only 2 of 1,751 women; moderate bleeding was recorded in 32 (4.2%) of women who used the THI-001 inserter and 29 (2.9%) of women who used (b) (4)
- Overall, the placement bleeding profile appears to be very similar for the two inserters.

IUD Removal Ease, Bleeding and Pain

IUS removal data is available for 326 Liletta subjects who were discontinued after successful placements. Not all discontinued subjects have IUS removal data because the IUS may have been removed by a non-study provider, the subject may have withdrawn consent or been lost to follow-up prior to removal, or have had a complete expulsion. The mean duration of exposure for Liletta subjects with IUS removal data was 13.8 months. About half of these subjects had IUS removal occur in the first year of use.

The IUS was removed by pulling on the IUS string in 96.6 % (315/326) of subjects. Difficulty with removal was for the following reasons (some subjects had multiple reasons noted):

- Required alligator forceps- 4
- Required use of other instrument- 3
- Required local anesthesia- 3
- Required ultrasound guidance- 2
- Removed in OR- 2 (Subject 101-0014 had laparoscopic removal and Subject 110-0030 had an ectopic pregnancy and exploratory laparotomy)
- Consent withdrawn so IUS could not be removed - 1

Bleeding related to removal was none in 80% of subjects, spotting in 15.6%, light bleeding in 2.8%, and moderate bleeding in 0.6%. Nulliparous and parous subjects were similar in reported bleeding during IUS removal, with no bleeding reported in 81% of nulliparous and 79% of parous subjects.

Cramping/pain related to removal was judged as none in 61.3% of all subjects combined, mild in 30.4%, moderate in 5.5%, and severe in 6 subjects (1.8%). Cramping was more common (45%) and more noticeable in nulliparous women compared to parous (32%).

Return to Fertility

See Section 6.1.5.1 and Table 18 for more details.

## 7.4 Supportive Safety Results

### 7.4.1 Common Adverse Events

AEs comprise any AE that occurred during the clinical study. An AE that is believed to be drug-related is called an adverse reaction (AR). The intensity of any AE was classified as mild, moderate, or severe. Nine events with Liletta and 1 with Mirena subjects were classified as life-threatening by the Applicant (discussed later). The following two tables show the overall AE profile for Liletta and Mirena as tabulated by the Applicant, and the second table lists in descending frequency the most frequent AEs believed by the investigator to be possible or definitely treatment (Liletta) related.

**Table 29: Applicant's Adverse Event Profile- Study L102 Safety Population**

| | Liletta | Mirena |
|---|---|---|
| **Total N (%) of women** | **1751 (100%)** | **159 (100%)** |
| **Subjects reporting at least one AE (%)** | **1,349 (77)** | **135 (85)** |
| **IUS- probably related** | **352 (20)** | **37 (23)** |
| **IUS-related** | **83 (4.7)** | **16 (10)** |
| **Maximum intensity** | | |
| **mild** | **545 (31.1%)** | **47 (29.6%)** |
| **moderate** | **634 (36.2%)** | **62 (39.0%)** |
| **severe** | **161 (9.2%)** | **25 (15.7%)** |

**Source: Modified by reviewer from Applicant Table 28, L102 CSR, page 127.**

**Medical Reviewer's Comment**

- The overall AE profile is not unusual for a contraception trial. Many of the common AEs are definitely not related to the IUS (such as nasopharyngitis, sinusitis, and bronchitis). Others may or may not be, such as urinary tract infection, vaginal infections, acne and headache. The above AE profile and Table 30 of most frequent AEs do not raise any safety concerns.



Reference ID: 3706342

**Table 30: Reviewer's Determination of Adverse Reactions ≥ 1.9%**

| Preferred Term | % Liletta Subjects (N= 1,751) |
|---|---|
| Acne | 10.7 |
| Vaginitis bacterial | 10.7 |
| Depression or mood change | 9.6 |
| Vulvovaginal mycotic infection | 9.3 |
| Abdominal pain or discomfort | 7.9 |
| Headache/migraine | 6.9 / 1.6 |
| Nausea or vomiting | 6.5 |
| Breast discomfort or swelling or discharge | 6.3 |
| Pelvic pain / dyspareunia/ | 6.0 / 5.7 |
| IUS expelled | 3.6 |
| Vaginal discharge | 3.5 |
| Ovarian cyst (symptomatic) | 3.4 |
| Abnormal bleeding / coital bleeding | 3.1 / 1.1 |
| Dysmenorrhea | 1.9 |

**Source: Reviewer table from JMP analysis of all reported adverse events- Study L102.**

**Medical Reviewer's Comment**

- The Liletta AR profile is not unusual for a contraception trial. The rate of these individual ARs is similar to that of Mirena and Skyla with the exception of ovarian cysts, where the labeled rates for Mirena and Skyla (all ovarian cysts) are 12.0 and 13.2%, respectively. When differences appear to exist, it is usually a result of how the events are recorded and either bundled together or split into smaller groups. This AR profile does not raise any safety concerns.

### 7.4.2 Laboratory Findings

### 7.4.3 Vital Signs and Weight Changes

Blood pressure (BP) was measured at baseline and 8 subsequent study visits. As shown in Table 31 below, there was very little change in systolic and diastolic values in subjects who continued for a full 36 months. Very similar small changes were noted in subjects who left the clinical trial at any time before 36 months. Most importantly, no subject had the IUS removed as the result of a change in BP.



Reference ID: 3706342

**Table 31: Mean BP (Systolic and Diastolic) Change at 36 Months-**

| | Liletta N=1571 (100%) | | Mirena N=159 (100%) |
|---|---|---|---|
| | Age 16-35 Mean Change | Age 36-45 Mean Change | Mean Change at 36 Months |
| Systolic blood pressure (mmHg) | Baseline- 114.2 Δ: -1.7 mm | Baseline- 117.2 Δ: +0.3 mm | Baseline- 115.0 Δ: -3.0 mm |
| Diastolic blood pressure (mmHg) | Baseline- 73.8 Δ: -0.7 mm | Baseline- 76.2 Δ: +0.6 mm | Baseline- 74.5 Δ: -0.8 mm |

**Source: Modified from L102 CSR, Table 80 and 81, page 194-5.**

**Medical Reviewer's Comments**

- An "increase in BP" was reported as an AE during the study in 5 women in the age 16-35 group and in 3 women in the older group. All 8 cases were considered by the investigator as not related to the IUS.
- Eighteen subjects had an AE reported as hypertension; 12 (0.8%) were in the Liletta age 16-35 group and 6 (4.0%) of the women age 36-45. None had the IUS removed as a result of the hypertension.
- This number of AE reports for "increase in BP" and hypertension does not raise a safety concern, especially since none of the subjects were discontinued from the clinical trial and the measurements were recorded over a 3-36 month span of time. Furthermore, there is no plausible physiological reason why a small daily release of LNG into the uterine cavity would adversely affect BP.

Weight

**No weight or BMI restrictions were in the protocol inclusion/exclusion criteria.** Weight was measured at baseline and Months 1, 3, 6, 12, 24, 30, and 36. Baseline weights (mean 159 lbs.) were lower in the younger women (age 16-35) compared to the age 36-45 group (mean 168 lbs.).

**Table 32: Subject Weights during Study L102**

| Time Point | | | LNG20 16-35 Yr Olds (N=1,600) | LNG20 36-45 Yr Olds (N=151) | LNG20 Total (N=1,751) |
|---|---|---|---|---|---|
| Screening | Visit | N | 1,596 | 151 | 1,747 |
| | | Mean | 159 | 168 | 159.8 |
| | | Median | 148.2 | 157.6 | 148.6 |
| | | Min, Max | 83.4, 379.7 | 94, 380.7 | 83.4, 381 |
| Month 12 | Visit | N | 666 | 110 | 776 |
| | | Mean | 163 | 173 | 164.3 |
| | | Median | | | 150 |
| | | Min, Max | 93, 408 | 106, 370.8 | 93.0, 408 |
| | Δ from Screening | N | 664 | 110 | 774 |
| | | Mean | 0.9 | 1.8 | 1.0 |
| | | Median | | | 1.0 |
| | | Min, Max | -99.8, 52.5 | -42.5, 30.8 | -99.8, 52.5 |
| Month 24 | Visit | N | 370 | 78 | 448 |
| | | Mean(SD) | 164 | 176 | 166.4 |
| | | Median | | | 153 |
| | | Min, Max | 97.4, 400 | 104, 388.5 | 97.4, 400 |
| Month 36 | Visit | N | 243 | 72 | 315 |
| | | Mean(SD) | 163 | 179 | 167 |
| | | Median | | | 152 |
| | | Min, Max | 107, 395 | 107, 335.6 | 107, 395 |
| | Δ from Screening | N | 241 | 72 | 313 |
| | | Mean(SD) | 2.4 (15.5) | 5.3 (16.8) | 3.1 (15.8) |
| | | Median | 3.0 | 3.3 | 3.0 |
| | | Min, Max | -65, 56 | -54, 56 | -65, 56 |

**Source: Modified from Applicant Table 82, L102 CSR, page 196.**

## Medical Reviewer's Comments

- Median weight values are better when assessing weight change over time because this will eliminate the impact of data outliers. The median gain in the 241 women aged 16-35 over 36 months was 3.0 pounds compared to 3.3 pounds in the 72 women aged 36-45. This change does not raise a safety concern.
- "Weight increased" was reported as an AE for 50/1600 (3.1%) of the group age 16-35 and 13/151 (8.6%) of the age 36-45 group.



Reference ID: 3706342

### 7.4.4 Electrocardiograms (ECGs)

Electrocardiograms were not performed for Study L102. Although several of the subjects had major medical conditions, it was not believed that the LNG-IUS would have an adverse effect on cardiac function.

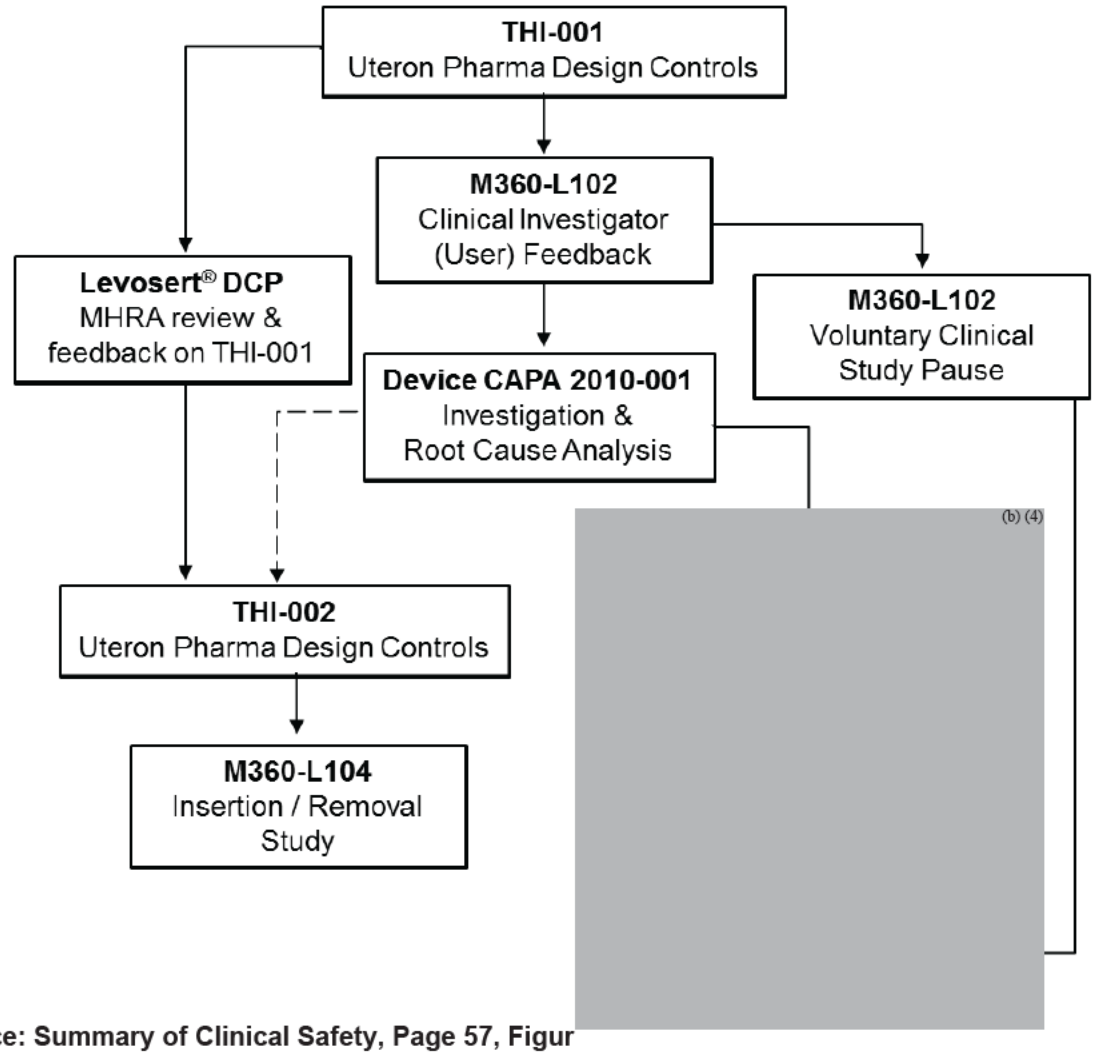
### 7.4.5 Special Safety Studies/Clinical Trials

As discussed with the Division during the Pre-NDA meeting and noted throughout this NDA, the to-be-marketed Liletta IUS was used throughout the clinical development program. However, two different inserters, THI-001 and (b) (4) were used in the phase 3 Study L102. In this section, overall safety data will be presented as well as safety data analyzed by inserter type.

L102 was initiated using a two-handed inserter (THI-001) for IUS placement. After 760 subjects were randomized using this inserter, recruitment into L102 was suspended due to investigator-reported difficulty in placement. While recruitment was suspended, (b) (4) After enrollment into L102 was completed, in preparation for the NDA submission, the Applicant decided to include a redesigned two-handed inserter as the proposed to-be-marketed inserter. T (b) (4)

The modified two-handed inserter (THI-002) is a redesign of the THI-001 inserter in which design improvements were incorporated. The evolution of the product design for Liletta, including its inserter, is characterized in Figure 4. The redesigned two-handed inserter (THI-002) was discussed with the Division at the Pre-NDA meeting and it was recommended that the Applicant conduct an inserter assessment (Study L104), given that there would be no phase 3 data using the THI-002 inserter. Per agreement with the Agency (dated December 9, 2013), the data from L104 was included in the 120-day safety update to the NDA to support the approval of Liletta with the new redesigned THI-002 inserter.

**Figure 4: Evolution of Liletta Product Design**




**Source: Summary of Clinical Safety, Page 57, Figur**

7.4.5.1 Overall Inserter Assessments

(b) (4)

who were sterilized, the insertion attempt was permitted at any time during the subject's menstrual cycle. In all other subjects, the placement attempt was required to occur within the first 7 days of the onset of the subject's menstrual cycle.

Liletta was placed in the subject's uterus by the study investigator using the SHI-001 inserter, with only a single placement attempt being allowed. Cervical anesthesia and dilation (Pratt dilator or os finder) were allowed as needed, and ultrasound guidance was permitted per protocol. On successful placement of the IUS (determined by ultrasound verification that the Liletta was within the uterus), the inserter was removed, and the tenaculum and speculum removed.

Liletta was removed approximately 5 to 15 minutes after IUS placement if, in the opinion of the investigator, it was clinically safe to do so. After IUS removal, the subject was observed for approximately 15 minutes to monitor AEs. The participant was sent home from the clinic when, in the opinion of the investigator, it was clinically safe to do so; per protocol, the IUS must have been removed prior to subject discharge from the clinic.

Subjects for whom IUS placement was unsuccessful were observed for at least 15 minutes to assess possible AEs.

All subjects who had cervical instrumentation (e.g., tenaculum placement, local anesthesia, dilation, or sounding), or who had Chlamydia or gonorrhea results, were required to have follow-up safety phone contacts approximately 2 and 7 days after the placement procedure to assess AEs. Additional appropriate follow-up was conducted, as needed, for subjects who had ongoing IUS placement- or removal-related AEs. There was no control or comparator group.

**Medical Reviewer's Comments**

- The study design and entry criteria were discussed with the Division and were acceptable. A total of 53 subjects were screened and 50 were enrolled; all 50 completed the study. The SHI-001 inserter was subsequently used with over 900 Liletta insertions in the phase 3 clinical trial.
- Brief demographic data showed: the average subject age was 28.8 years [range 19-44]; most subjects were White (68%) or African American (26%); 14% reported Hispanic or Latino ethnicity. A total of 31 (62%) subjects were nulliparous and 19 (38%) were parous. Average weight was 165 pounds [range 114-269] and BMI 27.2 [range 19-42].

**Study Insertion Results:**

Successful placement of the IUS occurred in 48 of 50 (96%) subjects. In all 48 subjects, intrauterine position of the IUS was verified by ultrasound after placement. Two subjects (1 nulliparous; 1 parous) had unsuccessful IUS placement. Per protocol, a second attempt was not allowed.

Safe IUS placement, defined as "no adverse event related to IUS placement," based on the incidence of IUS placement-related AEs, occurred in 41 of 50 (82.0%) subjects (84% nulliparous, 79% parous). Successful IUS placement and AE-free IUS placement



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combined was performed in 39 (78%) subjects (81% nulliparous, 74% parous). Local anesthesia administration to the cervical lip for tenaculum placement was employed in 28 (56.0%) subjects, with only 3 subjects (all nulliparous) requiring additional anesthesia for discomfort related to sounding or IUS placement. Cervical dilation during IUS placement was performed in 3 subjects (6%), including 2 (6.5%) nulliparous women and 1 (5.3%) parous woman.

Investigator assessment of IUS placement was evaluated: IUS loading was considered *"easy"* in 49 (98.0%) cases and neutral in 1 case. IUS placement was classified as *"easy"* in 44 (88.0%) subjects while the placement was considered "difficult" in only 4 (8.0%) subjects. There were 2 (4%) unsuccessful placements.

No IUS expulsions occurred during the brief (15+ minutes) post-insertion observation period. IUS removal was accomplished without difficulty by pulling the IUS string in all 48 (100.0%) subjects who had successful IUS placement.

Subject response was evaluated by a question regarding IUS insertion asked just after the placement procedure but before removal *"Based on your experience with the IUD insertion today, would you have an IUD inserted in the future for birth control that would last 2 years or more?"* Of the 48 subjects who completed the questionnaire, 44 (91.7%) subjects were willing to have IUS placement in the future for birth control that would last 2 years or more.

**Medical Reviewer's Comments**

- One of the two unsuccessful placements was due to an unintended withdrawal of the IUS at the time the inserter was removed from the uterus in a nulliparous subject. The other occurred in a parous subject due to the inability of the sound to pass an anatomical ridge in the cervix after which, per protocol, no attempt was made to place the IUS into the uterus with the inserter.
- The IUS placement within the inserter and then within the uterine cavity showed acceptable results. One shortcoming of this study is the short time that the IUS remained in the uterine cavity before removal, which led to little data on the risk of expulsion shortly after insertion.
    - For Study L104 with inserter THI-002, the IUS remained in place for at least 24 hours before removal.
- Subsequent data from the large L102 trial showed that with first attempts using the SHI-001 inserter, 11.8% of subjects needed cervical dilatation for IUS placement compared to 6% in this small study.
- Thirty-one of the 50 women were nulliparous and the results in both groups are comparable. It is not surprising that the 3 women requiring additional anesthesia were nulliparous.



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**L103 Study Safety Results:**

Bleeding and cramping/pain that occurred during the IUS placement and removal procedures were recorded separately from treatment-emergent adverse events (TEAEs).

Bleeding:

Bleeding was observed during IUS placement in 29 subjects (58.0%) with 16 subjects (32%) experiencing only spotting and 10 subjects (20%) experiencing light bleeding. Three (6%) subjects experienced moderate or heavy bleeding. Bleeding during IUS removal was evaluated in all 48 subjects. No bleeding was observed during IUS removal in 36 (75%) subjects. In the 12 subjects who experienced some bleeding during IUS removal, spotting was observed in 10 subjects and light bleeding in 2; no moderate or heavy bleeding was reported. None of the subjects reported any bleeding after discharge from the Placement Visit.

Cramping/Pain:

Some level of cramping and/or pain was reported in 47 (94%) of the 50 subjects who underwent an IUS placement procedure. A total of 32 (64.0%) subjects reported mild pain, including 16 (52%) nulliparous and 16 (84%) parous subjects. Moderate pain was reported in 11 (22%) women and severe pain in 4 (8%) subjects. The 2 subjects who had an unsuccessful IUS placement reported mild pain.

Cramping/pain was reported by 8 of the 48 subjects who underwent IUS removal. Seven of the 8 subjects experienced mild cramping/pain while 1 subject reported moderate cramping/pain. There were no reports of cramping and/or pain during the follow- up period after the placement/removal study visit.

Treatment-Emergent Adverse Events:

At least one TEAE was reported in 12 (24%) subjects. The only AE reported for more than 1 subject was metrorrhagia, which was reported for 5 subjects. Other AEs reported for nulliparous subjects (each reported for 1 subject) were back pain and syncope. Other AEs in parous subjects (each reported for 1 subject) were dysmenorrhea, dyspareunia, vulvovaginal pain, application site bleeding, sensation of low back pressure, myalgia, headache, syncope, and nausea. All AEs were mild, with the exception of 3 moderate events (back pain, fainting sensation, and dyspareunia) reported in 2 subjects.

Nine subjects (18%) experienced AEs related to IUS placement, with metrorrhagia being the most frequently reported placement-related event in 5 subjects. Five other events related to IUS placement (each reported for 1 subject) were back pain, syncope, bleeding from tenaculum site, sensation of low back pressure, and dysmenorrhea. AEs related to IUS removal were reported in 6 (12%) subjects and consisted of metrorrhagia (5 subjects) and dysmenorrhea (1 subject).

No deaths or other SAEs were observed in this study, and no subject discontinued the procedure due to an AE.

(b) (4)

7.4.5.1.2 Study M360-L104: THI-002 Inserter Study

**Study Design:**

This was a phase 1, open-label, unblinded, multi-center (6 US sites) study to assess the safety and performance of a modified two-handed inserter (THI-002) in 100 healthy female subjects age 18-45. After consent was obtained, screening procedures (including urine pregnancy testing and testing for sexually transmitted infections) were performed, entry criteria confirmed, and eligible subjects were enrolled. Each subject received a Liletta IUS, placed in the uterus by a study Investigator using the THI-002 inserter. A second attempt at placement of the LNG20 IUS was allowed, as long as both attempts were on the same day. Vaginal ultrasonography was performed after placement to confirm successful placement of the IUS. The subject then returned in approximately 24 hours to have the IUS removed. A Visual Analog Scale (VAS) was used for subject pain assessment immediately after uterine sounding and immediately after IUS placement. A VAS score was obtained just before IUS removal to assess average pain experienced over the prior 24 hours. After the placement attempt, subject acceptability of the procedure was assessed. Each investigator also assessed the acceptability of the Instructions for Use with the THI-002 inserter by completing a questionnaire.

All subjects had a safety follow-up phone contact approximately 7 days after the placement procedure to assess any latent AEs. Additional appropriate follow-up was conducted for subjects with unresolved IUS placement- or removal-related AEs. The study enrolled 100 women between 4 February 2014 and 24 March 2014; 57 were nulliparous and 43 parous.

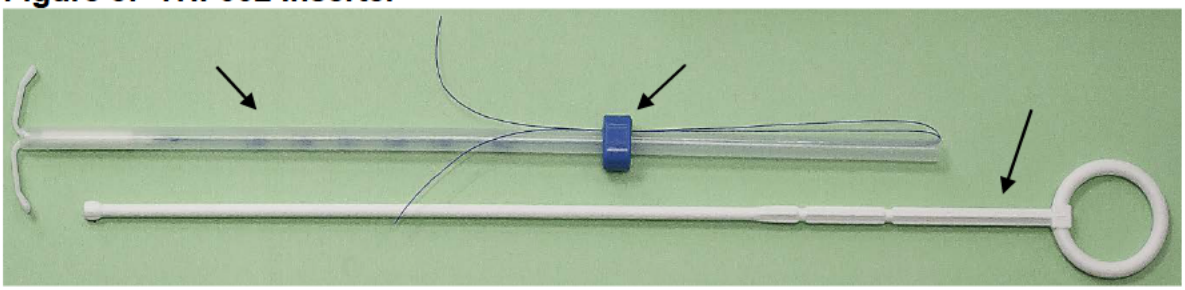
**Medical Reviewer's Comments**

- The Applicant, Medicines360, intends to market the Liletta IUS with an optimized two-handed inserter (THI-002). The THI-002 inserter was not used in the pivotal phase 3 L102 clinical trial and therefore the current study was designed to assess the performance of the THI-002 inserter for placing Liletta in nulliparous and parous women ages 18 to 45 years old.
- The protocol changes requested by the Division in the Type B Pre-NDA Meeting on September17, 2013 were incorporated into the final study protocol in Amendments 1 (November 2013) and 2 (December 2013).
- The inclusion/exclusion criteria were acceptable and enrolled women at low risk of pelvic infection.
- The THI-002 inserter has three components: a (b) (4) inserter tube (b) (4) flange, and a (b) (4) plunger (also referred to as an insertion rod). The product package contains the Liletta IUS partially pre-loaded at the top of the insertion

tube with the vertical stem located within the tube and the arms in a horizontal position (so that the product is in a T-shape). The IUS thread is pre-loaded through the insertion tube. THI-002 inserter included an insertion rod, all packaged in a single-use sterile pouch within a box. See Figure 5.

- All of the six Principal Investigators were directly trained by Mitchell Creinin, MD, Ob-Gyn Professor and Chairman at UC-Davis, on how to use the inserter.

**Figure 5: THI-002 Inserter**



Inserter tube: left arrow; Flange: middle arrow; Plunger: right arrow.

**Analysis Populations:**

There were 2 populations used for insertion analyses:

1. ITT: all subjects who had an attempted IUS placement, regardless of outcome. This population was also used to evaluate safety. N = 100 women.
2. PP (per protocol): a subset of the ITT that excludes subjects with major protocol deviations. There were none, so this population is the same as the ITT group.

**Study Insertion Results:**

95 of 100 subjects had a successful placement of Liletta with the first attempt. Four of the 19 "difficult" placements in Table 33 below were due to the IUS coming out of the uterus when the inserter tube was withdrawn and therefore considered failed initial insertions. One subject was discontinued after an unsuccessful first attempt because of cervical canal abnormalities from a previous myomectomy as well as a premature release of the IUS. Four subjects (2 parous, 2 nulliparous) with an unsuccessful placements had successful placement with the second attempt making an overall 99% successful placement rate.

The overall mean age for subjects was 30.3 [range 19-45] years. The majority of women (57%) were nulliparous, and 43% were parous. The study population was 78% White, 9% African American and 13% other; 15% subjects were of Hispanic ethnicity. The mean subject BMI was 28.7 $kg/m^2$ [range 18.7-56.5] with a BMI of 30-39.9 in 21% and ≥ 40 in 9% of the subjects.

**Table 33: Difficult Insertions in THI-002 Study**

| Subject ID | Age | Parity | Finding | Result/Comment |
|---|---|---|---|---|
| **Unsuccessful First Insertions** | | | | |
| 102-8011 | 31 | P2 | **Difficult** Cx* sounding | **Unsuccessful** insertion |
| 108-8001 | 44 | G3P1 | IUS* to fundus; IUS struck in inserter tip upon withdrawal | Success on later insertion |
| 133-8011 | 27 | G0 | IUS stayed in the inserter tube after insertion. Bleeding present. | Success on later insertion |
| 140-8003 | 30 | G0 | Multiple attempts because IUS stuck in flexible inserter. | Success on second attempt 3 wks later. |
| 140-8017 | 38 | P2 | Inserter too rigid. IUS stuck in tube with first try. | Success on second attempt 8 wks later. |
| **Other Difficult Insertions** | | | | |
| 108-8005 | 28 | P1 | Cx stenosis + tube kink/bend. Rigid dilation needed | **Difficult** placement |
| 108-8015 | 44 | P5 | Os finder needed; tube too flexible. | **Difficult** placement |
| 108-8021 | 29 | G0 | Os finder needed; narrow Cx.<br>3 tries to load IUS in inserter. | **Difficult** placement |
| 133-8010 | 25 | G0 | 5 tries at placement; IUS did not stay in inserter tube pre insert. | **Difficult** placement IUS in inserter. |
| 108-8004 | 41 | G2P0 | IUS reloaded >2. Tight Cx; inserter tube* kink-bending. | IUS was placed |
| 108-8022 | 33 | P4 | Full bladder; voided; **US* used**; then IUS inserted. | Distended bladder |
| 108-8027 | 21 | G0 | Small Cx with tight canal. | Successful insertion |
| 133-8003 | 21 | G0 | Narrow canal; IUS had to be reloaded into inserter tube | Successful insertion |
| 140-8004 | 31 | G0 | Inserter too flexible. | Success after >1 try. |
| 140-8009 | 31 | P1 | Rigid dilatation used. Inserter tube kinked. | Success after multiple attempts. |
| 140-8016 | 32 | G1P0 | Rigid dilatation used, then sounded easily. Inserter caught on internal os. | Success after multiple attempts. |
| 140-8018 | 26 | G0 | Inserter too flexible. Difficulty thru the internal os. | Success after multiple attempts. |
| 140-8020 | 31 | G0 | Inserter too flexible. Difficulty thru the internal os. | Success after multiple attempts. |
| 150-8006 | 43 | P7 | Pratt dilator used. **US guidance used.** Previous LEEP procedure. | Cx stenosis; placement done. |



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***Cx = cervix. IUS = intrauterine system. Tube = inserter. US = ultrasound.**

**Source: Reviewer table from 21 narrative reports (2 subjects had 2 narrative reports) from Section 14.2.2 in the L104 Study Report.**

Cervical anesthesia:

Local cervical anesthesia administration was used prophylactically according to investigator preference in 44 (44%) subjects: 30 (53%) nulliparous and 14 (33%) parous. About two-thirds (66%) of prophylactic cervical anesthesia was by local cervical injection (lidocaine; N= 29) and one-third (34%) was topical (benzocaine spray; N= 15) used on all subjects at the one particular site (#102). Three sites used no cervical anesthesia for their combined 45 subjects. When local cervical anesthesia was used prophylactically it was more frequently applied for nulliparous than for parous subjects (77% vs. 43%, respectively).

**Medical Reviewer's Comment**

- The use of cervical local anesthesia clearly depended on the site preference with one site using topical benzocaine for all 15 subjects, 2 other sites using local lidocaine for 29/30 subjects, and 3 sites using no local anesthesia for 56 subjects.

Cervical Dilation:

Rigid cervical dilation for IUS placement was performed during first placement attempts with a total of 18% of subjects; at all six sites, the percentage ranged from 10 to 26.7%. This included 18 subjects, with 12 (21%) nulliparous women and 6 (14%) parous women. The majority of subjects (61%; N= 11 of 18) for which dilation was performed required low grade dilation using an os finder. A Pratt dilator was used in 7 cases.

Ultrasound Guidance:

Ultrasound was used to aid placement for two subjects: 108-8022 (33 year old G7P4) and 150-8006 (43 year old G7P7).

Ease of Placement:

See Table 33 above. Ease of placement of the IUS with the THI-002 was assessed by the clinician using a standardized questionnaire. IUS placement with the THI-002 was classified as "easy" in 55 (55%) subjects, "neutral" in 24 subjects and "difficult" in 19 subjects for the first placement attempt. Four "difficult" placements were due to the IUS being withdrawn at the time of the inserter removal and therefore resulting in failed insertions. The "difficult" rating was very similar for nulliparous (19.3%) and parous (18.6%) subjects. Of these 21 "difficult" attempts, however, 16 had a successful first placement of the Liletta IUS. The reasons for a difficult insertion are listed here (a subject could have more than one reason):

- Requirement for one or more attempts with the same inserter to get through the cervical canal because of a significant problem with the inserter (13 subjects)
  - Inserter "too flexible" to easily pass through the cervical canal

- Inserter tube kinking
- Inserter tube too rigid (1)

- IUS remaining in the inserter upon inserter withdrawal from the uterus (4 subjects)
- Difficulty loading the IUS into the inserter and having it remain in place correctly (4 subjects); the IUS hemispherical dome continued to slip or be pushed into the inserter tubing, the tubing would catch on the ridges within the cervical canal and the IUS could not be passed through the canal. The IUS dome is intended to make the loaded inserter pass more easily through the canal.
- Need for rigid dilation to larger than expected diameter because of difficulty with the placement (3 subjects)
- Need for ultrasound guidance (2 subjects)
- Inability to pass the inserter into the cervical canal because of stenosis (unable to successfully dilate in 1 subject).

IUS Removals:
IUS removal was accomplished without difficulty by pulling on the IUS strings in 100% of the 98 subjects who had an IUS removal visit. Two subjects did not have removal visits, one that had unsuccessful IUS placement and one that experienced presyncope after leaving the study clinic and had the IUS removed in an emergency department later that day without any complications.

VAS Pain Scores:
For the first IUS placement attempt, VAS scores for pain were generally of moderate intensity. The mean VAS pain scores for immediate post-sounding were 43 (±23) mm. Nulliparous subjects had higher VAS pain scores post-sounding of 49 (±24) mm compared to parous subjects 36 (±21) mm. Immediately post-placement, the overall VAS score increased to 48 (±27) mm. Post -placement VAS scores increased to 57 (±26) mm for nulliparous subjects but remained essentially unchanged at 35 (±24) mm for parous subjects. The mean VAS pain scores for the 24 hours prior to IUS removal were 15 (median 8.0) mm for the entire subject population; 20 (median 14.0) mm for nulliparous subjects and 9 (median 3.5) mm for parous subjects [Sponsor Table 13, THI-002 CSR, pg 60].

Subject Acceptability:

Immediately after the procedure, subjects were asked, "*Based on your experience with the insertion process, are you willing to have another LNG20 IUD inserted in the future?"* The response was favorable for 88% of subjects.

Investigator Assessment of the Instructions for Use:

The THI-002 inserter Instructions for Use assessment questionnaire was completed by the 14 health care providers who performed placements and indicated that 5 (36%) found the instructions for performing insertions to be "very helpful," 7 (50%) "helpful" and 2 (14%) "average."



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**Medical Reviewer's Comment**

- The sample size of 14 for the instructions is too small to draw any meaningful conclusions.

**L104 Study Safety Results:**

Bleeding and cramping/pain during insertion and removal procedures were recorded separately.

Bleeding:
Bleeding was seen during IUS placement in 59 subjects, with 31 subjects having only spotting, 20 light bleeding and 8 moderate bleeding; no heavy bleeding was noted. The pattern for nulliparous and parous subjects was similar. Bleeding during IUS removal was evaluated in 98 subjects; no bleeding was recorded in 90 of 98 women. In the other 8 women, only spotting was observed.

Cramping/Pain:
Some level of cramping and/or pain was reported in 87 of the 100 subjects during the first insertion attempt.

**Table 34: L104 Cramping/Pain with Insertion and Removal**

| Cramping/pain | IUS Insertion (N= 100)<br>57 nulliparous; 43 parous | IUS Removal (N= 98) |
|---|---|---|
| None | 13 ( 0 nulliparous) | 60 |
| Mild | 36 (18 nulliparous) | 36 (25 nulliparous) |
| Moderate | 46 (35 nulliparous) | 2 (2 nulliparous) |
| Severe | 5 ( 4 nulliparous) | 0 |

**Source: Reviewer table modified from L104 CSR Table 27, page 80.**

**Medical Reviewer's Comments**

- The findings for bleeding and cramping/pain associated with IUS insertion and removal do not raise any safety signals or concerns as these side effects are expected with IUS placements. The sample size was only 100 women, so further data will be helpful from postmarketing sources following approval and marketing.
- Nulliparous subjects had more spotting/bleeding and cramping/pain with IUS insertion and more spotting and cramping/pain with IUS removal. However, there was no heavy bleeding in any subject; and severe cramping was reported with 4 nulliparous and 1 parous subjects during IUS insertion.

Treatment-Emergent Adverse Events (TEAE):

At least one TEAE was reported in 41 subjects. 31 AEs were considered related to the IUS with abdominal pain (20), vaginal bleeding (17), pelvic discomfort (4) and uterine pain (4) the most common. Parous women (37%) reported more IUS-related AEs compared to nulliparous (26%) with vaginal bleeding (30% vs 7%) and abdominal pain (26% vs 16%).

AEs related to IUS removal were reported in only 7 subjects: 6 reports of vaginal bleeding, 1 with uterine pain, and 1 with abdominal pain. Five of the subjects were parous and 2 were nulliparous.

In this short, limited study, there were no cases reported of uterine perforation, uterine hemorrhage (severe bleeding), uterine infection, PID or fungal urogenital infection. There were no IUS expulsions, perforations or SAEs related to the IUS in the 99 women for whom data was available. There was one report of an SAE of gastroenteritis in a 22 year old nulliparous woman that started the day after the IUS was removed; she was hospitalized for 48 hours and the event was not considered related to the IUS. Two other TEAEs are noted in the reviewer's comment that follows.

**Medical Reviewer's Comments**

- One nulliparous subject (140-8002) had a vasovagal reaction (recorded as presyncope) after she left the clinic following the placement procedure. She went to an emergency room where the IUS was removed. She received no other treatment and the event quickly resolved. The Investigator considered the event to be related to the IUS procedure and moderate in severity. Although the subject did not have the protocol-specified removal, the 7-Day follow-up was completed. The ease of placement was recorded as "*neutral*", cervical anesthesia or dilation was not used, and the subject had moderate cramping/pain. The subject reported a post-placement VAS score of 47.0 mm which was less than the mean of 56.2 mm in the nulliparous study population; so the "presyncope" reaction was delayed after the time of the IUS insertion.
- Another subject (140-8007) had a vasovagal reaction of moderate severity at the time of the IUS insertion; the episode resolved and the IUS was left in place.

**Medical Reviewer's Summary Comments**

- The IUS placement within the inserter and then within the uterine cavity showed mixed results.
- The TEAEs were those commonly experienced and expected with IUS insertions and removal. There were no SARs. There were, however, some findings that were notable and related to the THI-002 inserter.
    - After sounding the uterine cavity, there was difficulty passing the inserter through the cervical canal in 13 women (8 nulliparous and 5 parous) due to problems with the flexibility or kinking of the inserter.



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- After placement of the IUS into the uterine cavity, in 4 women the IUS was pulled back out with removal of the THI-002 inserter (2 nulliparous and 2 parous).
- There was repeated difficulty loading the IUS into the inserter in 4 women before placement.
- There was failure to place the IUS in 5 women (3 parous) on the first visit; placement was successful at a later date in 4 of these women (2 nulliparous and 2 parous). A second attempt was not made with the fifth woman because of a scarred and misshapen cervical canal possibly from a previous myomectomy.

- As noted above, the THI-002 inserter is the one the Applicant plans to use with their IUS, if approved and marketed; it was not used for any of the 1,751 subjects in Study L102. Because of this significant limitation and the notable findings above, it is reasonable that more safety data should be collected post approval with a formal agreed upon method. See this reviewer's recommendations in Section 1.2 Risk Assessment.

#### 7.4.6 Immunogenicity

Not applicable for this submission.

### 7.5 Other Safety Explorations

#### 7.5.1 Dose Dependency for Adverse Events

Not applicable, as the Sponsor is seeking approval of only one dose of LNG for the IUS.

#### 7.5.2 Time Dependency for Adverse Events

Evaluation for time dependency for AEs was noted with respect to several IUS-related AEs, such as PID and expulsions, and has been discussed in previous sections.

#### 7.5.3 Drug-Demographic Interactions

This product is indicated for use only in women of childbearing age. No other special populations were studied. The Sponsor had good representation of nulliparae and overweight and obese women in the phase 3 trial.

#### 7.5.4 Drug-Disease Interactions

No drug-disease interactions were studied.



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### 7.5.5 Drug-Drug Interactions

No drug-drug interaction studies were performed for this NDA application. Class labeling for progestins includes a section on drug-drug interactions, which will be included in the Liletta label.

### 7.5.6 Bone Mineral Density

This was not studied by the Applicant primarily because it was not required and because there are studies in the medical literature that have addressed this topic.

## 7.6 Additional Safety Evaluations

### 7.6.1 Human Carcinogenicity

No human carcinogenicity trials were indicated or performed.

### 7.6.2 Human Reproduction and Pregnancy Data

The transfer of LNG from the maternal plasma via breast milk to the infant was studied after insertion of an LNG-containing IUS initially releasing 20 µg/day of LNG (Mirena). The study revealed a lower LNG percentage transfer from maternal serum to breast milk (about 12%) and relatively higher percentage LNG transfer from breast milk to the infant's serum (about 75%). The total amount of LNG excreted per day in 600 mL breast milk is low and is approximately 0.2% of a daily dose of 20 µg.

**Medical Reviewer's Comments**

- LNG is transferred to the infants' circulation via the breast milk; this is noted in labeling for Mirena and other LNG contraceptives, and will be labeled for Liletta.
- In general, no adverse effects have been found from the small amounts of progestins that pass into the breast milk of nursing mothers.

### 7.6.3 Pediatrics and Assessment of Effects on Growth

No effect on growth or development has been observed in infants breast fed by users of a 20 µg/day LNG-IUS (Mirena), compared with infants of copper IUD users.

#### 7.6.3.1 Pediatric Research Equity Act (PREA)

In accordance with PREA, all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. PREA applied to this application because the duration of use specified in the indication differs from that of Mirena.



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Based on the intended use of the product, the Applicant proposed to address the PREA requirements for Liletta as follows:

- Because contraception is not needed and Liletta will not be indicated in pre-menarchal patients, the Applicant requested a (b) (4) waiver from pediatric study requirements for such patients.
- Because the reproductive physiology of post-pubertal adolescent females less than 17 years of age is similar to that of other women of reproductive age, the Applicant requested that the PREA requirements for post-menarchal pediatric patients be deemed fulfilled by extrapolation of adult data.

The PeRC (Pediatric Review Committee) PREA subcommittee met on December 3, 2014. The PeRC recommendation was that they "agreed with the (b) (4) waiver and assessment presented in all pediatric patients for this product."

**Medical Reviewer's Comment**

- The Division accepted the (b) (4) waiver for premenarchal girls and data extrapolation from adult to postpubertal females recommended by the PeRC. No PREA postmarketing requirement will be needed for this submission.

### 7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Not applicable for this submission.

## 7.7 Additional Submissions / Safety Issues

### 7.7.1 The 4-Month (120-Day) Safety Update Report

The data cutoff for the original NDA submission was July 12, 2013. A 4-Month Safety Update Report (PSUR) was received on August 27, 2014 and covered the Study L102 safety update through May 30, 2014 providing an additional 46 weeks of data.

This submission included the following information:

- A Clinical Study Report (CSR) for Study M360-L104, which evaluated the performance of the to-be-marketed THI-002 inserter.
- Updated tabular listing of clinical studies reflecting the "completed" status of Study M360-L104
- L102 safety update
- Updated literature references

#### 7.7.1.1 Study L104: THI-002 Inserter

This clinical study used only the modified IUS inserter design (THI-002) that the Applicant plans to use for insertion with Liletta, if approved.

**Medical Reviewer's Comment**

- The study design and results are discussed in detail in Section 7.4.5.1.2 above.

7.7.1.2 Study L102 Safety Update

The Applicant's summary of the safety update follows verbatim:

"Overall, the conclusions from the data provided in this safety update are similar to the conclusions made and presented in the original NDA submission:

1. No clinically significant, unexpected findings have been observed with Liletta in the overall population.

2. No clinically significant differences in safety profile have been observed with Liletta when analyzed by age (18 – 30 years of age, 31 – 35 years of age, 36 – 45 years of age).

3. No clinically significant differences in safety profile have been observed with Liletta with regard to parity status (parous vs nulliparous).

4. No clinically significant differences in safety profile have been observed with Liletta when analyzed by BMI (BMI < 25.0, 25 to < 30.0, 30.0 to < 40.0, and ≥ 40.0).

5. No clinically significant differences in the safety profile were observed with Liletta with regard to race (white versus non-white).

All AEs in the cumulative dataset were expected for the study population and size and duration of the study. The only SAE of note was the expected occurrence of 2 additional ectopic pregnancies; however, the incidence of this rare AE is still well within the expected ectopic pregnancy rate for women who use intrauterine contraception."

**Medical Reviewer's Comments**

- There were three additional ectopic pregnancies: the 2 listed in the 120-day update and one reported in a 15-day expedited report, SD-84, Stamp date January 5, 2015. All 3 occurred during Year 2 of use. These cases are discussed below following the other comments on the Safety Update.
    - During the first 3 years of IUS use up to December 19, 2014, there have been 2 intrauterine pregnancies (1 in Year 1; 1 in Year 2) and 4 ectopic pregnancies (1 in Year 1 and 3 in Year 2). The overall pregnancy rate is very low for both intrauterine and ectopic pregnancies. Because it is known that the relative number of ectopic pregnancies is higher with IUS contraception compared to all other forms of contraception, the number of ectopic pregnancies is not a concern or unusual.
- There were no additional deaths.
- There were no new cases of sepsis, PID or endometritis.
- There were no additional perforations.
- There were no cases of breast cancer at any time up to the May 30, 2014 date.



Reference ID: 3706342

- There were 13 additional expulsion reports: 7 in nulliparous women and 6 in parous women; 4 in the THI-001 group (1 in Year 1; 3 during Year 4) and 9 in the SHI-001 group (8 in Year 1; 1 in Year 2).
    - The previous expulsion rate was 2.8%; the revised rate adding the 10 cases that occurred within the first 3 years is 3.4%. This is comparable to the 3.2% rate reported in the Skyla label and the 4.9% rate stated in the Mirena label.
- There were 12 additional reports of ovarian cysts, with one subject discontinued from the study because of the cyst. This is an expected adverse reaction and in line with the previously reported ovarian cyst rate of 2.7%; the revised 3.4% rate is well within the expected range.

Additional Ectopic pregnancies:

1. Subject 101-2098: 32 year old G4P4 female with the IUS for 21 months. She presented with vaginal bleeding and severe lower abdominal pain, positive pregnancy test, and ultrasound findings of a normal IUS placement and a complex left adenexal mass. She was taken to the OR and a laparoscopic left salpingectomy plus suction of the hemoperitoneum performed. The IUS was removed vaginally and she was discharged home following the surgery (without an overnight stay).
2. Subject 135-2025: 21 year old G0P0 female with the IUS for 17 months. She presented with lower abdominal pain and feeling lightheaded. A pregnancy test was positive (β-hCG 1065) and an ultrasound showed no IUP but free fluid in the abdomen. The intrauterine IUS was removed, laparoscopy was performed with normal fallopian tubes visualized and the right ovary cauterized. Pathology reports showed no chorionic villi on endometrial or ovarian tissue, but chorionic villi was identified in the peritoneal blood. She was treated with methotrexate after the surgery. Diagnosis was an extrauterine pregnancy.
3. Subject 133-2091: 27 year old G0P0 female with the IUS for 21 months. She had a positive home pregnancy test, came to the clinic where a transvaginal ultrasound showed a normal IUS placement and no intrauterine pregnancy. The IUS was removed. A small (8x8x10 mm) right adenexal mass was identified; serial β-hCG values were 925, 875, and 798. She elected to be treated with methotrexate 93 mg IM and was closely followed. No major surgery was needed and the diagnosis was that of a resolving right ectopic pregnancy with a follow-up plan of serial hCG testing and repeat methotrexate if indicated.

#### 7.7.1.3 Extent of Additional Exposure

As of the cutoff date of December 19, 2014, the estimated exposure accumulated for Liletta is shown in Table 35. Further data is being collected as the study is ongoing and the Applicant (b) (4)

**Table 35: Liletta Exposure by Year and Cumulative- Study L102, Age 16-45 Years**

| | Liletta Exposure Update (Women-Years) | Liletta Exposure (July 2013) (Women-Years) |
|---|---|---|
| Year 1 only | 1,448 | 832 |
| Year 2 only | 1,094 | 470 |
| Year 3 only | 468 | 348 |
| Year 1-3 (cumulative) | 3,010 | 1,650 |

**Source: Medical reviewer from Safety Update, Table 19, page 32 and December 19, 2014 update.**

**Medical Reviewer's Comments**

- Because L102 is an ongoing study, overall exposure to Liletta has increased with each safety update. The NDA submission and updated cumulative exposure is shown in the above table. Year 4 data is new as no subjects had completed 4 years of exposure by July 2013.

# 8 Postmarket Experience

No commercial marketing experience has been obtained for Liletta because this product has not yet been marketed in any country although a similar product (Levosert) is approved for marketing in several European countries (see Section 2.1 Product Information).

# 9 Appendices

## 9.1 Literature Review/References

The Applicant submitted several articles from the peer-reviewed medical literature. They support the use, efficacy and safety of LNG-releasing IUSs. Safety issues of ectopic pregnancy, infection, ovarian cysts, uterine perforation and IUS expulsion are well covered and addressed.

**Medical Reviewer's Comment**

- The medical literature was comprehensive; the data from the Liletta clinical trial and the labels for other LNG-containing IUSs were also noted and covered by this clinical review of the NDA for Liletta.

## 9.2 Labeling Recommendation

Labeling is currently under review. The proposed label is undergoing revisions in order to better harmonize with the current class IUS labels. There were no significant areas of disagreement for the Liletta label. Section 8 titled Use in Specific Populations Section was revised in accord with the new Pregnancy and Lactation Labeling Rule

(PLLR) guidance. Section 8.1 is Pregnancy, Section 8.2 is Lactation, and next is Section 8.4 Pediatric Use. Agreement on the label was reached between the Division and the Applicant on February 24, 2015.

## 9.3 Advisory Committee Meeting

No Advisory Committee Meeting was indicated or held.

## 9.4 Schedule of Study Events

See Figure 6 on the following page.

**Study Events**

| Enrollment Day 1 | Months 1, 3, 6 | Month 9 Contact | Month 12 | Month 15 Contact | Month 18 | Month 21 Contact | Month 24 | Month 27 Contact | Month 30 | Month 33 Contact | Month 36 | Month 39 Contact | Month 42 | Month 45 Contact | Month 48 | Month 51 Contact | Month 54 | Month 57 Contact | Month 60 Term/ED | Safety FU 30-43 days | Continued FU |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| X | | | | | | | | | | | | | | | | | | | | | |
| X | | | | | | | | | | | | | | | | | | | | | |
| X | | | | | | | | | | | | | | | | | | | | | |
| X | | | X | | | | X | | | | X | | | | X | | | | X | | |
| X | X | | X | | X | | X | | X | | X | | X | | X | | X | | X | X | |
| X | | | | | | | | | | | | | | | | | | | | | |
| X[4] | | | X[4] | | | | X[4] | | | | X[4] | | | | X[4] | | | | X[4] | | |
| X | | | X[5] | | | | X[5] | | | | X[5] | | | | X[5] | | | | X[5] | | |
| X[6] | X[6] | | X[6] | | X[6] | | X[6] | | X[6] | | X[6] | | X[6] | | X[6] | | X[6] | | X[6] | | |
| X[7] | X | | X | | X | | X | | X | | X | | X | | X | | X | | X | X | |
| X | | | X | | | | | | | | | | | | | | | | X | | |
| X | | | | | | | | | | | | | | | | | | | | | |
| X | | | | | | | | | | | | | | | | | | | | | |
| X | | | | | | | | | | | | | | | | | | | | | |
| X | | | | | | | | | | | | | | | | | | | | | |
| X | X | | X | | X | | X | | X | | X | | X | | X | | X | | | | |
| X | | | | | | | | | | | | | | | | | | | | | |
| | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | |
| | | | | | | | | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| | X | X[10] | X | X[10] | X | X[10] | X | X[10] | X | X[10] | X | X[10] | X | X[10] | X | X[10] | X | X[10] | X | | |
| X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| | X | | X | | X | | X | | X | | X | | X | | X | | X | | X | X | |
| | | | | | | | | | | | X | | X | | X | | X | | X[11] | | |
| | X | | X | | X | | X | | X | | X | | X | | X | | X | | X | | |
| | | | | | | | | | | | | | | | | | | | X | | |
| | | | | | | | | | | | | | | | | | | X[13] | X[14] | X | |
| X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X[15] | X[15, 16] |

uled Month (±7 days for Months 1 and 3)
to enrollment and anticoagulants for 30 days
ed physical exam
6.11 guidelines
jects ≤ 25 years old
d sexual partners since last tested or last visit
on same day prior to insertion
T, bilirubin
se

[10] If change in sexual partner is noted during phone/email contact bring in for unscheduled G/C testing prior to next clinic visit [11] Not required if Early Determination <36 months
[12] By palpation or visualization (ultrasound if missing strings)
[13] For contact prior to Month 60 Term/ED discuss contraception options for discontinuation visit
[13] Initiation of primary method of contraception when possible
[15] Appropriate monthly contact by phone or clinic visit to follow ongoing AEs and return to menses. If no return to menses within 3 months of IUS removal/expulsion, refer for evaluation and continue follow-up until diagnosis is made
[16] For women desiring pregnancy follow by phone contact every 3 months up to one year

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

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/s/

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DANIEL DAVIS
02/23/2015

LISA M SOULE
02/23/2015
I concur with Dr. Davis' review and recommendation for approval of NDA 206-229.