CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206229Orig1s000

SUMMARY REVIEW

Deputy Division Director Summary Review

Date	February 28, 2015
From	Audrey Gassman, MD
NDA #	206229
Applicant name	Medicines360
Date of receipt of original submission	April 30, 2014
PDUFA goal date	February 28, 2015
Proprietary name/established name	Liletta/levonorgestrel-releasing intrauterine system
Dosage form/strength	Sterile intrauterine system/52 mg levonorgestrel drug reservoir
Proposed Indication	Prevention of pregnancy (b) (4) for up to 3 years
Action	Approval

Material reviewed/consulted	Names of discipline reviewers
CDTL Review	Lisa Soule, MD
Medical Officer Review	Daniel Davis, MD
Statistical Review	Kate Dwyer, PhD Mahboob Sobhan, PhD
Pharmacology/Toxicology Review	Krishan Raheja DVM, PhD Alexander Jordan, PhD
Clinical Pharmacology Review	Li Li, PhD Myong-Jin Kim, PharmD
ONDQA Review	Nina Ni, PhD Moo-Jhong Rhee, PhD
ONDQA Biopharmaceutics Review	Kelly Kitchens, PhD Tapash Ghosh, PhD
Product Quality Microbiology Review Team	Denise Miller, PhD Neal Sweeney, PhD
DMEPA	Denise Baugh, PharmD, BCPS Irene Chan, PharmD, BCPS Kellie Taylor, PharmD, MPH
DMPP	Shawna Hutchins, MPH, BSN, RN Marcia Williams, PhD LaShawn Griffiths, RN, MSHS-PH, BSN
OPDP	Carrie Newcomer, PharmD
OSI	Roy Blay, PhD Janice Pohlman, MD, MPH Kassa Ayalew, MD, MPH
CDRH Device Review (Inserter)	Veronica Price, PhD Biomedical Engineer Becky Robinson, PhD Herbert Lernder

CDTL=Cross-Discipline Team Leader
OND=Office of New Drugs
DMEPA=Division of Medication Error Prevention and Analysis
ONDQA=Office of New Drug Quality Assessment
DMPP=Division of Medical Policy Programs
OPDP=Office of Prescription Drug Promotion
DPP=Division of Professional Promotion
DDTCP=Division of Direct-to-Consumer Promotion
OSI=Office of Scientific Investigations
SEALD=Study Endpoints and Labeling Development Team
CDRH – Center for Devices and Radiologic Health

1. **Introduction**
2. **Background**
3. **CMC**
4. **Nonclinical Pharmacology/Toxicology**
5. **Clinical Pharmacology**
6. **Clinical Microbiology**
7. **Efficacy/Statistics**
8. **Safety**
9. **Advisory Committee Meeting**
10. **Pediatrics**
11. **Other Relevant Regulatory Issues**
12. **Labeling**
13. **Decision/Action/Risk Benefit Assessment**

1. Introduction

The Applicant, Medicines360, submitted NDA 206229 on April 29, 2014, to obtain marketing approval for a new intrauterine system (IUS). The proposed indication for this IUS is prevention of pregnancy, (b) (4), for up to 3 years. For the purposes of this review, this new levonorgestrel IUS will be referred to by the proposed tradename, Liletta.

This IUS contains approximately 52 mg of levonorgestrel, a synthetic progesterone in a reservoir on a polyethylene T-frame. Liletta has an in vitro release rate of 18.6 µg/24 hours of LNG, which is lower than a currently approved LNG-containing IUS, Mirena (NDA 21-225). Intrauterine systems are designed to be long acting, reversible contraceptive products. IUS requires a healthcare provider to insert and remove the system from the uterus. The first levonorgestrel IUS, Mirena, was initially approved more than 20 years ago in the US and is marketed in over 100 countries. Compared to Mirena, Liletta has the same drug load. Liletta has an initial daily in vitro release rate of 18.6 µg LNG, which decreases to 16.3 µg/day at one year, 14.3 µg/day at two years and 12.6 µg/day at three years after insertion. There are currently two other FDA approved IUS on the US market, Skyla (which contains LNG), and the copper-containing Paragard. The Paragard and Skyla labels do not specify any parity restriction, and have been used in nulliparous women.

Levonorgestrel, a synthetic progesterone, has a long history of use in many approved hormonal products in the US. These indications include both contraception (oral, intrauterine, and implants) and menopausal hormone therapy. The levonorgestrel component of Liletta exerts its contraceptive effect locally in the uterus primarily by:

- thickening the cervical mucus, and
- preventing the proliferation of the endometrium during the menstrual cycle

Liletta contains 52 mg of levonorgestrel combined with polydimethylsiloxane (PDMS) to form a silicone (b) (4), (b) (4). A PDMS membrane (b) (4) surrounds the reservoir, which is mounted

on a vertical stem of a low density polyethylene T-frame, compounded with barium sulfate (BaSO4) for radio-opacity. A polypropylene monofilament thread is attached to an eyelet at the base of the T-frame for IUS removal.

Comment: The presence of barium sulfate for radio-opacity allows easier identification of the IUS via imaging once inserted.

The primary efficacy and safety study was designated as M360-L102. In this study (referred to as L102 hereafter), two inserters were used to place the IUS in the uterine cavity. A two-handed inserter (THI-001) used initially. After feedback from the investigators about patient discomfort, the trial was temporarily halted for 20 months, and a single handed inserter (SHI-001) was evaluated in a phase 1 trial - Study L103. Subsequently, the L102 phase 3 trial was completed in the remaining 900 subjects with the SHI-001 inserter. (b) (4) , the Applicant opted to market Liletta with a modified two-handed inserter (THI-002). As the THI-002 inserter was not used in the primary efficacy trial, the Division requested the Applicant conduct another phase 1 clinical study (L104) to characterize the functionality and safety of the THI-002 inserter. The Applicant submitted study reports for L102, L103 and L104 to support efficacy and safety of Liletta.

Comment: Liletta is regulated as a combination drug-device product. The T-body contains levonorgestrel, a synthetic progesterone drug, and the non-drug components of Liletta and inserter are considered a device. CDRH was consulted to evaluate the functionality of the device portion of Liletta, and CDRH's consult review is summarized in section 11 of this memo entitled, "Other Relevant Regulatory Issues".

The Applicant is seeking approval of Liletta in reproductive aged women, (b) (4) , for up to three years of use. No preclinical studies were conducted by the Applicant; all studies to support safety of LNG and materials used in the manufacture of Liletta and the inserter were provided by reference to published literature or to studies for which the Applicant had right of reference. In addition to the three clinical trials mentioned above, the Applicant also submitted (at the request of the Division) a final study report for Liletta conducted for European registration (under the name Levosert-20). This trial was not conducted by the Applicant, but by another sponsor who evaluated the therapeutic equivalency for the indication of menorrhagia.

Comment: The Applicant did not sponsor or participate in the Levosert-20 trial for approval in Europe. However, the Applicant submitted the clinical study report for the Levosert-20 trial at the Division's request to provide supportive safety data for the Liletta application.

The pivotal phase 3 trial M360-L102 (Trial L102) formed the basis of efficacy for Liletta. Trial L102 was a multicenter, randomized, open-label, two-arm, parallel-group phase 3 trial conducted at 40 sites in the US. The trial enrolled 2,150 generally healthy women between the ages of 16 and 45 years. The phase 3 trial initially included a Mirena arm to address European regulatory requirements; this arm was discontinued after 159 subjects

were enrolled. This arm was not intended to support any comparative claims in the US. The total treatment duration for subjects who received Liletta was up to 3 years. The primary efficacy variable was the unintended pregnancy rate calculated using the Pearl Index (PI) in women ages 16 to 35 years during years 1, 2, and 3 individually and cumulative 2-year and 3-year PIs in which backup contraceptive was not used. Life Table Analysis of pregnancy rates over successive years were also calculated and presented as secondary estimates. Trial L102 met the Division's standard recommendation for contraceptive products that efficacy evaluation be based on a minimum of 10,000 cycles of exposure in the first year of use.

As the to-be-marketed inserter (THI-002) was not used in Trial L102, the Division requested a study to evaluate the to-be-marketed inserter. The final report from the phase 1 study of this inserter (L104) along with a phase 1 study of a one-handed inserter used in the phase 3 clinical trial (L103) were submitted as supportive. In addition, the final study report and data from a study that evaluated Liletta for menorrhagia, conducted by a different sponsor, was submitted to provide additional supportive safety data.

No significant safety or efficacy issues were identified during the review of this application for the Liletta product or the to-be-marketed inserter (THI-002). There are no outstanding clinical pharmacology, nonclinical toxicology, or chemistry, manufacturing and control (CMC) issues. Final acceptable product labeling was submitted by the Applicant on February 24, 2015. Both the primary Clinical Reviewer and the Cross Discipline Team Leader (CDTL, who also was the Clinical Team Leader) have recommended approval of this Application; I concur with their recommendations.

2. Background

The Applicant initiated discussions of Liletta for the indication of prevention of pregnancy with the Division of Reproductive and Urologic Products (now, the Division of Bone, Reproductive, and Urologic Products) in 2009. Key discussions and agreements during drug development are outlined below.

The pre-IND discussion on the development program for was captured in meeting minutes dated September 10, 2009. At that time, the Division agreed that no new nonclinical studies would be required and that a 505(b)(2) approach relying on published literature and the FDA findings of safety for Mirena (levonorgestrel IUS) was an acceptable approach. The Applicant noted that the phase 3 trial would include a small arm of Mirena users to satisfy European regulatory requirements for safety comparison. The Division commented that the acceptability of the Applicant's IUS Pearl Index would be based on its own merits, not on a comparison to Mirena and claims regarding superiority to Mirena would not be allowed. (b) (4)

IND 105,836 for Liletta was opened on November 21, 2009, with submission of a protocol for Study M360-L102. This protocol (hereafter referred to as Trial L102) proposed a multicenter, randomized, open-label, two-arm, parallel group phase 3 trial to evaluate an intrauterine system that releases 20 µg/day (Liletta). A comparator arm was proposed using an approved LNG IUS (Mirena). In the protocol, the goal was to enroll a minimum of 1,530 Liletta users and 400 Mirena users who were nulliparous or parous and between the ages of 16 and 45 years. The primary efficacy cohort would include women between 16 and 35 years of age. The primary efficacy variable was the pregnancy rate as calculated by the Pearl Index (PI) with a 95% confidence interval in the modified to treat (MITT) population. The MITT population was defined as all subjects who were randomized and for whom there is at least one report of pregnancy status after insertion of the IUS. This Pearl Index was to be used to establish efficacy for the first 2 years of use. The Pearl Index during years 3, 4, and 5 was a secondary endpoint (b) (4)

Comment: The phase 3 protocol for Trial L102 was not submitted under a Special Protocol Assessment (SPA), although agreement was reached on the majority of efficacy and safety evaluations proposed.

The Agency reviewed the protocol for Trial L102 and determined it was safe to proceed for the purpose of opening a new IND. Several comments and recommendations were sent to the Applicant on January 26, 2010, including the following:

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

The Statistical Analysis Plan for Trial L102 was submitted in August 2010 and reviewed by the Statistical review team. At that time, the statistical review noted that the previous comments had been adequately incorporated. Other protocol amendments were submitted in 2010; no further comments were conveyed to the Applicant.

The Applicant submitted a protocol for a phase 1 Study L103 in November 2011 to evaluate the safety (b) (4) single-handed inserter (SHI-001). The Division did not understand the rationale for this proposed study and a teleconference was held in January 2012. During this call, the Applicant explained that the current two-handed inserter (THI-001) being used in the phase 3 Trial L102 wa (b) (4) temporarily stopped the phase 3 trial L102 (b) (4) Study L103 would evaluate SHI-001 in 50 women, at least 30% nulliparous and confirm the location of the IUS insertion using ultrasound. The IUS

would then be removed 5-15 minutes after insertion. Following acceptable results from L103, the Applicant intended to use the SHI-001 inserter in the remainder of the Trial L102 participants.

A guidance meeting was held in June 2012 to discuss CMC, clinical and regulatory issues. The Applicant proposed changes to the drug product manufacturing process and use of a new manufacturing facility as well as required testing for raw materials that control release of the active pharmaceutical ingredient (LNG). (b) (4) The Applicant proposed that the initial NDA submission for (b) (4) years of use would include the Division's requested minimum of 10,000 28-day cycles and a minimum of 200 women ≤ 35 years of age. In addition, agreement was reached that the efficacy would be analyzed as a whole although two different inserters were used in the phase 3 trial, since the type of inserter would not be expected to impact efficacy. The Division also agreed that safety data from L103 (the phase 1 study of the SHI-001 inserter) would not be included in the safety database, but would be included in a separate final study report. Finally, safety data from a European menorrhagia trial of the LNG IUS conducted by a separate business entity with whom the Applicant has partnered would be provided as a study report, but these safety data would not be integrated with that for the Applicant's contraception trial.

Comment: The Applicant requested a guidance meeting regarding development of the (b) (4) *. Although the meeting was denied because of insufficient information in the package, additional guidance was provided to the Applicant.*

A revised SAP for Trial L102 was submitted in September 2012, and the Division requested that cycles in which a back-up contraceptive method was used be excluded from the life table analysis, and that additional subgroup analyses be done based on inserter type used. The Division also disagreed with the Applicant's plan that subject-reported pregnancies that were not followed-up would not be considered on-treatment pregnancies; the Division will evaluate all pregnancies and make its own determination, typically relying upon a "worst case" approach when data are limited. In a further revised SAP submitted in February 2013, the Applicant accepted the Division's recommendations.

A Type B Pre-NDA Meeting held on September 17, 2013, discussed the format and content of the NDA for Liletta. The Applicant clarified that its NDA would rely upon its own clinical data, nonclinical data for which it had right of reference, and information from the public domain (published literature) and it would not reference approved Mirena labeling. During the discussion, the Division made the following key comments or agreements:

- A 505(b)(2) NDA submission was acceptable.
- The proposed label should be submitted in the PLR format.
- Upon initial consideration, Pediatric Research Equity Act (PREA) does not apply to this product as it would request a partial waiver for girls <12 and extrapolate data for girls 12-15. The Division noted that girls as young as 16 were enrolled in

the phase 3 trial L102. However, the Division recommended the Applicant that he final determination regarding PREA would be made during the review cycle.

- The Applicant stated that they planned to seek an indication of 3 years of use (b) (4). The primary endpoint would be the Pearl Index in women aged 16-35 years. The Division stated that the acceptability of the Pearl Indices at Years 1 and 3 as well as the cumulative three year Pearl Index would be important considerations.
- The Applicant stated that the to-be-marketed inserter (THI-002), a revised two-handed inserter, had not been studied in the phase 3 trial L102. The Division requested the Applicant conduct a phase 1 study to support use similar to L103 for the single handed inserter (SHI-001). The Applicant was asked to test the new THI-002 in at least 100 women, of whom 50% would be nulliparous. Insertion instructions should be similar to anticipated labeling and feedback from patients and providers should be collected regarding the insertion process as well as any adverse events. CDRH asked the Applicant to provide a root cause analysis and bench testing to show that any problems identified in the phase 3 inserters have been addressed and are unlikely to occur with the THI-002 inserter, as well as providing stability data on the THI-002 inserter.
- The Applicant also agreed to provide the requested information from a European menorrhagia study using the Liletta IUS (tradename Levosert-20 in Europe); and to submit the Levosert-20 data as SAS transport files. The Division also requested that the submission discuss any significant inquiries about safety or efficacy that arose during the Medicines and Healthcare Products Regulatory Agency (MHRA) review of the Liletta IUS used for the European menorrhagia study. The Sponsor will also include narratives for other important IUS-related adverse events (e.g., perforations, expulsions).

The protocol for the Phase 1 study L104, that would evaluate the new inserter (THI-002) was submitted in October 2013 and proposed the IUS be retained after insertion for at least 24 hours to allow for evaluation of post-insertion events. The Division provided comments on the protocol for L104, and agreed to accept this study report at the time of the 120-day safety report as the data were not critical for approval of Liletta.

NDA 206229 was submitted on April 29, 2014, as a standard application and was filed with no issues identified.

3. ONDQA

Liletta (levonorgestrel-releasing intrauterine system) is a drug product-device that consists of a T-shaped polyethylene frame (T-frame) with a (b) (4) reservoir (hormone (b) (4) around a vertical stem. The reservoir consists of a mixture of levonorgestrel and polydimethylsioxane (PDMS) formed from a silicone base and is covered by a PDMS membrane. The active ingredient, levonorgestrel, is physically (b) (4).

The drug substance in this IUS is levonorgestrel USP, a well characterized synthetic progestin. Each levonorgestrel (LNG) drug reservoir contains 52 mg of USP grade [redacted] LNG. The Applicant supplied a DMF [redacted] for levonorgestrel as well as batch data for drug substances used in the manufacturing of clinical and stability batches of the drug product.

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 the product radio opaque. A blue polypropylene monofilament removal thread is attached to the eyelet at the end of the vertical stem of the T-frame.

Each drug product is placed in an inserter tube used for insertion into the uterus. The inserter tube consists of [redacted] that is printed with a graduated scale and is supplied with a [redacted] flange and [redacted] pusher. The drug product and inserter tube are packaged in a pouch constructed of [redacted] and [redacted] on one side and [redacted] on the other,

The Chemistry Reviewer evaluated the LNG substance in the core and the excipients and components of the device including the [redacted] core, the membrane (tubing), the T-body, the removal thread and the inserter. The ONDQA reviewer determined that the DMFs that supported the manufacturing of the drug substance and [redacted] were adequate and that residual solvent and impurity levels comply with USP and ICH requirements. In addition, the ONDQA reviewer evaluated the non-compendial excipients, which included two novel [redacted] excipients, and found them to be acceptable from a CMC perspective.

The Chemistry reviewer also made the following comments on the drug release process for this IUS to assure batch to batch consistency in her review dated December 19, 2014, "The drug product under review is a very unique dosage form. IUS is designed to have a [redacted] to release LNG in a constant manner over a period of 3 years. The particle size distribution of the drug substance may have significant impact on the drug release profile of the drug product. A laboratory scale study was conducted to determine the potential impact of LNG particle size on the drug product manufacturing process and the capability to meet acceptance criteria for drug reservoirs and drug reservoir assemblies. Five [redacted] LNG batches were included in this study, three of which covered the proposed range of the LNG particle size specification. Results from this study demonstrate that the dispersion of LNG drug substance within this proposed range in the [redacted] is adequate to produce drug reservoirs and drug reservoir assemblies that meet the proposed acceptance criteria for critical quality attributes (reservoir mass uniformity, LNG assay, LNG related substances, and LNG drug release). Thus, the proposed acceptance criterion for the particle size distribution deems adequate."

The Chemistry reviewer provided comments on the carton/container labeling, which were conveyed to the Applicant. After review of the Applicant's submissions for Liletta, on

December 19, 2014, the Chemistry reviewer noted the following deficiencies that precluded Approval are summarized below including:

- Specification of the drug product has not been satisfactorily established due to pending recommendations for sterility (Microbiology Review) and drug release rate (Biopharmacology Review). Also, functionality of the inserter has not been satisfactorily determined.
- The Office of Compliance has not made an overall "Acceptable" recommendation for the manufacturing facilities.
- Issues on labels and labeling have not been resolved.

The ONDQA Biopharmaceutics Review team evaluated the drug release method development and the proposed drug release acceptance criteria. The review focused on the drug release method development and the proposed dissolution specification value. On January 16, 2015, the Biopharmaceutics reviewers concluded, that, "From the Biopharmaceutics perspective, NDA 206229 for Liletta® (levonorgestrel releasing intrauterine system) is recommended for approval."

Subsequently, the Applicant submitted acceptable labeling, and the Microbiology, Biopharmaceutics and CDRH reviewers made "Approval" recommendations. The Office of Compliance made an "Acceptable" recommendation on February 5, 2015. Following resolution of these issues, the Chemistry reviewer provided an addendum to her review dated February 11, 2015, in which she concluded, "All previous unresolved issues have been satisfactorily resolved. Therefore, from the ONDQA perspective, this NDA is recommended for approval."

The Chemistry, Microbiology, and Biopharmaceutics reviewers did not recommend any postmarketing commitments or requirements. For more detail on the CDRH reviewer, please refer to Section 11 of this review.

Comment: There are no outstanding CMC, Device Manufacturing, Biopharmaceutics issues. I concur with the "Approval" recommendation of the ONDQA review teams.

4. Nonclinical Pharmacology/Toxicology

The Liletta product was developed based on experience with the approved contraceptive products containing levonorgestrel, including the IUS products, Skyla and Mirena. For this Application, all of the nonclinical studies to establish the safety of the active ingredient (levonorgestrel) and the materials used in the manufacture of the drug reservoir and inserter were supported by reference to published literature or studies for which the Applicant has right of reference.

After review of the submitted reference materials from the Applicant, the pharmacology/ toxicology reviewer concluded in their December 2014 review that, "No additional nonclinical studies aside from those committed by the sponsor and were agreed by the Division in the Pre-NDA meeting are recommended." In their December 10, 2014 review, Pharmacology/Toxicology team did not identify any outstanding issues from

their perspective and recommended approval of NDA 206229. In an addendum to their review on February 11, 2015, the Pharmacology/Toxicology review team also confirmed that no additional postmarketing commitments or requirements were requested or planned.

Comment: I concur with the approval recommendation of the pharmacology/toxicology review team that there are no outstanding pharmacology/toxicology issues.

5. Clinical Pharmacology

No dedicated clinical pharmacology studies were conducted with Liletta. Levonorgestrel (LNG) systemic exposure was assessed in a subset of subjects in the pivotal phase 3 trial (Study M360-L102). The Clinical Pharmacology review team evaluated LNG exposure data from the phase 3 trial. In that sub-study, a total of forty subjects (obtained in both obese and non-obese subjects) had PK sampling at Day 7 and Months 1, 6, 12, 18, 24 and 30 months after insertion, and 243 subjects had sampling done upon completion of 36 months of use. The Clinical Pharmacology reviewer also evaluated the criteria and assay performance for the active ingredient, LNG, and found the bioanalytical methods to be acceptable.

No drug-drug interaction studies were conducted as the contraceptive effect of LNG is considered local to the uterus. In addition to the sub-study of the phase 3 trial, three supportive study reports that contained pharmacokinetic data (Phase 1 Studies M360-L103 and M360-L104 and a study of patients with menorrhagia Study Levosert-20) were also reviewed by the Clinical Pharmacology reviewer.

The Clinical Pharmacology reviewer, Dr. Li Li, made the following overall recommendation in her review dated January 30, 2015, that, "The Office of Clinical Pharmacology/ Division of Clinical Pharmacology 3 (OCP/DCP3) has reviewed the clinical Pharmacology sections of NDA 206229. The submission is acceptable from a Clinical Pharmacology point of view pending agreement of labeling recommendations in the package insert." No postmarketing commitments or requirements were recommended by the Clinical Pharmacology review team.

In an addendum the January 2015 review, the Clinical Pharmacology reviewer stated that, "The Clinical Pharmacology review of NDA 206229 (DARRTS, January 30, 2015) stated that NDA 206229 was acceptable provided that an agreement is reached between the sponsor and the Division regarding the language in the package insert labeling. The final agreement on clinical pharmacology sections was reached on Feb 23, 2015 and there are no pending issues from the Office of Clinical Pharmacology. The highlights of the prescribing information and Clinical Pharmacology relevant sections of the final agreed upon package insert labeling are included in Section 2 of this addendum." The Clinical Pharmacology reviewer then stated that they recommended NDA 206229 was acceptable for Approval.

Comment: I concur with the overall Approval recommendation of the Clinical Pharmacology review team. At this time, labeling text for the Clinical Pharmacology section has been agreed to with the Applicant. Therefore, there are no outstanding Clinical Pharmacology issues.

6. Clinical Microbiology

A consult to the Product Quality Microbiology group was requested to provide advice on the Applicant's proposed microbiological validation, sterility test method and package integrity for release. The Microbiology reviewer completed her consult on January 23, 2015. The consult stated that the Applicant's amendment to address microbial limits testing was acceptable and stated, "This application is recommended for approval from a quality microbiology perspective."

Comment: I concur with the approval recommendation of the Microbiology Review team that there are no outstanding issues related to microbial specifications.

7. Efficacy/Statistics

Contraceptive efficacy data for Liletta was obtained from one multicenter, randomized, open-label, phase 3 clinical trial, Trial M360-L102, entitled, "A Phase 3, Randomized, Multi-Center, Open-Label Study of a Levonorgestrel-Releasing Intrauterine System (IUS) (20 µg/day) and Mirena® for Long-Term, Reversible Contraception up to 5 years." The trial was conducted at the 29 study sites in US. The objective of the trial was to evaluate the efficacy and safety of Liletta in nulliparous and parous women ages 16 to 45 years. Women would be randomized to receive Liletta or Mirena in a 4:1 ratio, with the exception of those over 35 years old, who would only receive Liletta.

Comment: A second arm of an approved US product (Mirena) was originally included in the phase 3 trial (L102). This arm was not requested by the Agency, but was included for the purpose of European marketing authorization. This arm was stopped after 159 subjects were enrolled as the Applicant realized they had sufficient comparative data to satisfy European authorities for potential marketing approval. Given the limited information from available from the Mirena arm, the collected data was used solely for supportive safety information.

Key entry criteria included women ages 16-45 years (those under 18 years of age required parental consent in addition to the informed consent) and regular sexual activity in a monogamous relationship for at least six months. Key exclusion criteria included breastfeeding, current pelvic inflammatory disease (PID) or a history of PID without subsequent intrauterine pregnancy, HIV positivity for the subject or partner, recent unresolved uterine, cervical or vaginal infection and history of bicornuate uterus or other uterine abnormality that resulted in distortion of the uterus or cervix incompatible with IUS placement. Notably, there were no exclusion criteria based on parity, weight or body mass index (BMI).

Investigators were selected for having prior experience placing IUSs. Supervised training was conducted on the IUS insertion and for both inserters used in the phase 3 trial. Insertion was performed within seven days after the onset of menses or at the end of the duration of another contraceptive method. Subjects were withdrawn after two failed insertion attempts or following complete or partial expulsion of the IUS or perforation.

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. Subjects recorded use of back-up contraception on a daily basis in the subject diary. Days for which no information regarding back-up contraception was recorded were considered days without such use. Pregnancy was defined as a positive blood or urine pregnancy test; site confirmation of reported pregnancies included urine pregnancy test or quantitative serum hCG at the study site and ultrasound. On-treatment pregnancy was defined as including those conceived during or within 7 days after use of the IUS. In addition, subjects were asked to use a daily diary to assess back-up contraception use, bleeding occurrence and intensity.

A total of 1,910 women were enrolled from 29 US centers in Trial L102, of whom1,751 (92%) had one placement attempt with Liletta. Demographics for Trial L102 was reported as a mean age of 27 years, with a mean BMI of 26.9 kg/m^2 with 57% of women being nulliparous. Ethnicity was reported as 78% Caucasian, 13% Black, 4% Asian and 4% other. The primary reasons for study discontinuation in Trial L102 after a successful placement of IUS were adverse events (9.2%) and loss to follow-up (5%). The number of subjects who finished at least 1 year, 2 year and 3 year study duration (MITT population) are 1286, 495, and 307, respectively using a cut-off date of May 30, 2014.

Inserter THI-001, a two-handed inserter, was used in 760 women from December 2009 through July 2010, with 731 successful insertions. The trial was suspended (b) (4) and resumed in March 2012 with SHI-001, a single handed inserter.. Use of the SHI-001 was initiated after a phase 1 trial (L103) to evaluate the (b) (4) inserter was completed and analyzed. SHI-001 was continued as the exclusive inserter for Liletta in 991 with 983 successful insertions until trial L102 was completed in April 2013.

Comments:

1. *The population studied in this phase 3 trial was determined by the clinical team to be acceptable and representative to the target population of women who would likely use Liletta in the US, with a reasonable representation of nulliparous women and women with higher BMI.*

2. *The to-be-marketed inserter (THI-002) was a redesign of THI-001 and is a two-handed inserter. A phase 1 study using the inserter was requested by the Division and the study (L104) was evaluated as part of the safety data.*

The primary efficacy endpoint was the Pearl Index in women with a 2 sided confidence interval (CI), calculated as X/E, where X = the number of on-treatment pregnancies and E=exposure time, calculated as the number of evaluable 28-day cycles of exposure, in accord with the usual calculation for hormonal contraceptives. For exposure time, only cycles with no back up contraceptive method recorded were included in the calculation. The final cycle of use (e.g., for subjects still on study when the Pearl Index was calculated) was considered complete if it was ≥ 23 days long, or if a pregnancy was conceived in that cycle.

The primary efficacy analysis was the MITT population defined as all subjects between 16 and 35 years of age who had a successful IUS insertion and at least one assessment of pregnancy status post-insertion. The MITT population for Liletta included 1,545 subjects. Information on back-up contraception used to exclude cycles was collected in daily diaries, missing data was imputed as no use of back-up contraception. (b) (4) After discussion with the Division, the plan was modified to seek three years of use.

Based on the decision to seek three years of use, the Applicant calculated the Pearl Indices for Years 1, 2, and 3 individually and cumulative Two-Year and Three-Year rates. The Applicant also performed life table analyses that did not exclude cycles in which back up contraception was used, and a secondary analysis using "absolute time" which excludes cycles in which back up was used, but then counts subsequent cycles after use in the total exposure. Life table rates were also calculated for sub-groups based on age, parity, race, body mass index (BMI) and inserter type.

There were 43 on-treatment pregnancies occurred in Liletta subjects. The 43 Liletta pregnancies were classified as follows:

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

In summary, a total of 6 pregnancies were determined by the Agency to be on-treatment during the three years of cumulative use of Liletta. Table 1 presents the primary Pearl Index results in the ITT group (all subjects) and in the MITT group (primary efficacy cohort) in women 16 to 35 years old who received Liletta in Trial L102.

Table 1: Pregnancy Rates for All Liletta Treated Subjects in M360-L102*

	Population	N	On-treatment Pregnancies	Number of Cycles	Pearl Index	95% Confidence Interval
Year 1	ITT MITT (Ages 16-35)	1,691 1,545	2 2	18,820 17,125	0.14 0.15	(0.02,0.50) (0.02,0.55)
Year 2	ITT MITT (Ages 16-35)	1,318 1.195	4 4	14,217 12,694	0.37 0.41	(0.10,0.94) (0.11,1.05)
Year 3	ITT MITT (Ages 16-35)	591 496	0 0	6,088 4,892	0 0	(0, 0.80) (0,0.98)
Year 1 to Year 3	ITT MITT (Ages 16-35)	1,691 1,545	6 6	39,018 34,711	0.20 0.22	(0.07,0.44) (0.08,0.49)

*Adapted from Table 4 of the Statistical review dated February 23, 2015

The statistical reviewer confirmed the calculations from the Applicant in the above table and also did not identify any issues in the Applicant's submission. The statistical reviewer also reviewed the Applicant's cumulative pregnancy rates in MITT population using Life Table approach and confirmed that they are 0.14 (95% CI: 0.04 to 0.57) for Year 1; 0.55 (95% CI: 0.24 to 1.23) for Year 2; and 0.55 (95% CI: 0.24 to 1.23) for Year 3. Of note, there were no pregnancies in women aged 36-45 years, and the PI estimate is zero.

In her statistical review dated February 23, 2015, the statistical reviewer stated that, "The PI point estimates and cumulative pregnancy rates using life table method were ≤ 0.55 and the upper bound of the 95% CI has not exceeded 1.23, a threshold generally considered acceptable for IUS contraceptives. Both analyses consistently demonstrated that LNG20 IUS was effective in preventing pregnancy for up to three years of product use." The Medical Officer reviewed the Pearl Indices and stated that, "The values calculated in the above table are virtually the same as the Applicant's, and represent an acceptable level of efficacy."

In the Medical Officer's review dated February 23, 2015, he stated that no per protocol (PP) calculations were done because only 3 subjects of the 1,545 subjects in the MITT population had a major protocol deviation that could have impacted efficacy outcome. He concluded that in his February review that, "I concur that the Applicant's determination of the PP findings would be virtually undistinguishable from the MITT population."

Life Table Pregnancy Rates: The Applicant's Life table pregnancy rates for the Liletta MITT population with no cycles excluded were also evaluated by the statistical and clinical reviewers as an efficacy analysis for cumulative pregnancy rates. Life table estimates may be more informative than the Pearl Index because these estimates are conditional probabilities over time that accurately incorporates total exposure. The Life table estimate for Years 1 through 3 in the MITT population demonstrated a cumulative pregnancy rate of 0.55 with a 95% CI (0.24, 0.77) and as previously mentioned, are included in labeling.

Comment: I concur with the Statistical reviewer and Medical Officer that the Pearl Index calculations from the MITT populations for Year 1 and Cumulative 3-Year Life Table calculations are acceptable as a demonstration of efficacy for Liletta and should be provided in product labeling.

Additional Key Secondary Efficacy Analyses:

Efficacy by Inserter Type: As previously mentioned, two different inserters were used in the phase 3 trial L102, THI-001 and SHI-001. THI-001 was used in 648 subjects and after investigator reported difficulty in placement, enrolled was suspended (b) (4) . Enrollment into the phase 3 trial was reinitiated and 952 subjects using the SHI-001 inserter. For both inserters, the proportion of nulliparous women was well above the Division requirement that the study enroll at least 20% nulliparous women. Five of the six on-treatment pregnancies occurred with use of the SHI-001 inserter and 1 pregnancy in a subject who had Liletta placed with the THI-001 inserter.

After review of the inserter data from the phase 3 trial L102, the Medical Officer commented in his February 2015 review that, "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."

Comment: I concur that there is no evidence that the to-be-marketed inserter, which is very similar to the THI-001 inserter, will have a significantly negative impact on efficacy. In terms of safety, please see the review of the phase 1 study of the new inserter (THI-002) in section 8 below.

Cumulative Pearl Indices evaluated by sub-group analysis (Parity, body mass index (BMI) and race): The clinical review team assessed the evaluable cycles by parity, BMI and race for Years 1, 2 and 3, cumulatively. After review, the Medical Officer concluded in his February 2015 review that, "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."

Comment: Although calculated through sub-group exploratory analyses, the lack of impact of BMI and obesity on the Pearl Indices is clinically important and the findings will be briefly summarized in the Special Populations sub-section of labeling.

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

- None
- Spotting
- Light
- Moderate

- Heavy

The Applicant determined that the reliability of subject recall over a three-month period for day-to-day bleeding and spotting was poor, Therefore, data on bleeding was collected from daily diaries in approximately 400 subjects who had at least one visit post-24 months in the trial L102. Cumulative interval bleeding data were collected in a summary question completed every three months through interview.

Bleeding was considered a treatment-emergent adverse event (TEAE) if the diary indicated that bleeding was heavier than when not using hormones. Amenorrhea was defined as the absence of bleeding throughout the reference period (90 days) being assessed analyzed the bleeding profile of Liletta as a secondary efficacy endpoint. The 28-day bleeding and spotting data are presented in Table 2. These data reflect all bleeding/spotting, regardless of whether "scheduled" or "unscheduled." Because the IUS insertion frequently occurred during menses, the first month data likely reflects this menstrual bleeding; data from Month 2 onward are more reflective of the effect of Liletta on bleeding patterns. The bleeding data collected from subjects is outlined by 28-day cycle in the table below:

Table 2: Bleeding Days per 28-Day Cycle (First 12 Cycles, then at Year 2)*

Cycle	N	Mean (SD)	Min	Median	Max
1	1,691	5.8 (5.2)	0	5.0	28
2	1,650	4.1 (4.8)	0	3.0	28
3	1,620	2.9 (3.9)	0	2.0	28
4	1,525	2.3 (3.3)	0	1.0	28
5	1,444	2.1 (3.1)	0	0	28
6	1,378	1.9 (2.9)	0	0	28
7	1,223	1.5 (2.6)	0	0	23
8	1,039	1.5 (2.7)	0	0	28
9	1,012	1.4 (2.6)	0	0	24
10	997	1.3 (2.3)	0	0	14
11	959	1.2 (2.4)	0	0	16
12	891	1.1 (2.2)	0	0	18
24	457	0.8 (1.6)	0	0	10

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

In addition to irregular bleeding and spotting, amenorrhea developed in approximately 19% of Liletta users by the end of the first year of use, in 26% by the end of the second year of use, and in approximately 38% of users by the end of year 3. The Medical Officer reviewed the data on bleeding, spotting and amenorrhea and reported that bleeding occurred more frequently after IUS placement and then diminished through the end of one year of use and then increased through 3 years of use.

The CDTL also evaluated the bleeding and spotting profile identified in the phase 3 trial L102 and concluded that, "The overall bleeding/spotting profile appears acceptable, with about 3-4 days per 28-day cycle by the second six month of use."

It was also noted that 248 of 255 women experienced menses with 3 months of Liletta removal. The clinical team concluded that these data on bleeding, spotting and amenorrhea were similar to data from other approved IUSs and did not represent a new trend that might lead to higher discontinuation rates for Liletta.

Comment: I agree with the clinical review team that it is important for healthcare providers and patients to be aware that LNG IUS products can alter bleeding patterns and result in spotting, irregular bleeding, heavy bleeding and oligomenorrhea. A summary of the data above on bleeding and spotting days as well as the rates of amenorrhea and return to menses will be included in labeling.

Other exploratory efficacy analyses of L102 that were reviewed included:

- Endometrial thickness sub-study – A subset of 50 subjects aged 16-35 years had endometrial thickness obtained at baseline and month 12. However, due to timing of study visits, insufficient samples were collected during the luteal phase to allow an informative assessment. The mean thickness identified was 3.8 mm.
- Residual levonorgestrel (LNG) content sub-study – an ex vivo assessment of IUSs that were removed or expelled for residual drug content
- Pharmacokinetic (PK) sub-study – The PK study enrolled 57 subjects aged 16-35 years of age who were enrolled in the primary phase 3 study (L102). The PK evaluation was designed to include as many obese (n=19) as non-obese subjects (n=21) who had serial sampling of LNG over the duration of use.
- Return to fertility - Subjects who discontinued from the trial and desired pregnancy (N = 42) were followed for up to 12 months to assess fertility after Liletta removal. 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.

Comments:

1. *No efficacy or pharmacokinetic issues were identified from these sub-studies*
2. (b) (4)
3. *The return-to-fertility data were reassuring and indicated that those subjects who sought pregnancy could do so relatively soon after discontinuing Liletta.*

Efficacy summary:

The efficacy database for Liletta was reviewed by the clinical and statistical review teams. Both the statistical and clinical review teams determined that Liletta had an acceptable Pearl Index for approval for the prevention of pregnancy for 3 years of use The CDTL concluded in her review dated February 25, 2015 that, "The contraceptive efficacy study conducted by the Applicant provides evidence of an acceptable level of efficacy for Liletta in the prevention of pregnancy. Although the PI increased from Year 1 to Year 2, no pregnancies occurred in Year 3, and the upper bound of the 95% CI for

each year remained ≤ 1.1. The overall pregnancy rate (upper bound) over the three-year course of treatment by life table analysis was 0.24 (0.77). Efficacy was similar regardless of parity, BMI or race."

Comment: I concur with the statistical reviewer, clinical reviewer and CDTL that the cumulative Pearl Index for the three years of 0.22 (0.08, 0.49) is acceptable for approval of Liletta.

8. Safety

The clinical review team focused their review on the primary safety database from the phase 3 trial L102. The primary safety database from L102 also included data provided in the 120 day update. The two phase 1 studies (L103 and L104) that evaluated the inserters were reviewed for safety, but in both, the IUS was removed shortly after insertion, so no long-term safety data were available from those studies. The European study of the Levosert-20 IUS phase 2/3 study for menorrhagia conducted in Eastern Europe that was conducted by a different Sponsor was also reviewed, but because the patient population was clinically different from the population for Liletta, the safety data were not included in the integrated safety summary for Liletta.

The safety database for Liletta is derived from phase 3 trial L102 and consists of a total of 1,751 women, of which 1,600 women were in the primary efficacy cohort (ages 16-35). A total of 1,412 women completed one year and 383 completed the three year trial. These women provided 21,553 28-day cycles (1,658 women-years) of use data, and 1,011 of women in the trial were nulliparous. This exposure exceeded the Division's requested safety cohort of 10,000 cycles in the first year of treatment with at least 200 women ≤ 35 years of age to complete three years of treatment with at least 20% of the population being nulliparous.

As the Applicant changed the type of inserter used in the phase 3 trial L102, safety data was also evaluated for adverse events related to insertion, by inserter type. For the phase 3 trial a total of 760 women received Liletta using the THI-001 inserter (two-handed) and 991 women received Liletta using the SHI-001 (one-handed) inserter.

Other supportive safety data were obtained from:

- Study Levosert-20: A phase 2/3 menorrhagia trial in 280 Eastern European women to investigate the efficacy of Levosert-20 (tradename for Liletta in Europe) for the treatment of heavy menstrual bleeding
- Study L103: A phase 1 study in 50 women to assess the (b) (4) SHI-001 (a single handed inserter) compared to the original two handed inserter (THI-001).
- Study L104: A phase 1 study in 100 women (57% nulliparous) to assess the safety and performance of a revised two handed inserter (THI-002).

Comment: Pooled safety data with the other submitted supportive studies was not done because there was only one large phase 3 trial for this NDA submission. The European study was not performed in the intended healthy population and therefore was considered

separate and supportive and the inserter studies had use of Liletta for less than 48 hours, so safety data was too limited to include in the pooled safety database. However, data from these studies was evaluated separately by the clinical review team.

Primary safety cohort (phase 3 trial L102):

In the phase 3 trial L102, a total of 1,751 women were enrolled and had a Liletta insertion attempt and formed the primary safety cohort. The safety population was generally healthy, 18 to 45 years of age who requested intrauterine contraception. In addition, safety data from the two inserters in phase 3 trial L102 were evaluated as pooled data, as well as separately, for adverse events that are considered insertion-related.

Comment: I concur with the Medical Officer and CDTL that the safety database was adequate to characterize the safety profile of Liletta for the proposed duration of 3 years of use.

Deaths, Serious Adverse Events and Discontinuations due to Adverse Events:

Deaths: One death occurred in Trial L102 – Subject 108-2191. This subject was a 30 year old woman who received Liletta using the SHI-001 inserter in March 2013. The subject had a 10-year history of "mild depression" and had been taking antidepressants for the past year. She reported no complaints or mood changes at her Month 1 visit, but committed suicide the next day. The investigator concluded that the suicide was not related to Liletta. The clinical review team reviewed the case report and concurred with the investigator that this suicide was not related to the IUS.

Non-fatal Serious Adverse Events (SAE):

SAEs occurred in 47 women (2.6%) who received Liletta. Selected potential serious adverse events (that may be related to study drug) are outlined in Table 3 below:

Table 3: Potential Serious Adverse Reactions in the safety database from L102*

Serious Adverse Reaction**	Liletta Safety Population N=1,751
Bipolar disorder exacerbation	6 (0.34)
Ectopic pregnancy	5(0.29)
Suicidal ideation	3(0.17)
Suicide attempt	2(0.11)
Ovarian cyst	2(0.11)
PID	2(0.11)
DVT	1(0.06)
Portal vein thrombosis	1(0.06)
Completed suicide	1(0.06)
Depression exacerbation	1(0.06)
Ischemic stroke	1(0.06)
Bilateral wrist laceration	1(0.06)

*Modified from Table 13 of the CDTL review dated February 25, 2015.
** Serious adverse reactions (SARs) were serious adverse events (SAEs) that were identified as possibly related to the IUS

Comments:

1. *There were a significant number of SAEs in the Psychiatric Disorder System Organ Class (SOC) and a number related to bipolar disorder, depression and suicidality. The clinical team observed that there was a high baseline of psychiatric disorders recorded in the study population at entry (>20%). Based on this limited safety data, without baseline psychiatric testing, it is difficult to determine if Liletta worsened these conditions. After review of the individual cases, it was deciding that labeling was the appropriate way to present the limited data on psychiatric disorders.*
2. *The above table included all potential serious adverse reactions that were related to Liletta. After further review of possible causality with the Applicant, the following SAEs were included in labeling: suicidality, exacerbation of depression and bipolar disorder, ectopic pregnancy, ovarian cysts and uterine perforation requiring laparoscopic surgery.*

Discontinuations for adverse events:

In the safety population for Liletta 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. 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%).

In his February 23, 2015 review, the Medical Officer evaluated the discontinuation adverse events and noted that, "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." He also noted that the numbers of lost to follow-up rates were reassuring and lower than many other contraceptive clinical trials.

A second analysis was performed to evaluate discontinuation for failed insertion. A total of 113 failed attempts to place Liletta were reported. Discontinuation from the trial after the first insertion attempt occurred in 30 subjects (28.3%) and in 7 subjects (9%) after the second insertion attempt. The Medical Officer stated that, "The small percentage of (total) subjects 2.1% (37/1,751 subjects) of the total enrolled subjects is acceptable given the large number of nulliparous subjects in the study."

Comment: I agree with the Medical Officer that the rates of discontinuation and reasons for discontinuation do not appear to demonstrate a new or worrisome trend for use of Liletta. In addition, I also agree with the clinical team that the most common adverse

events resulting in discontinuation of Liletta in the phase 3 trial L102 be incorporated into labeling.

Common Adverse Reactions

Any adverse event that was believed to be drug-related was classified as an adverse reaction. The most common adverse reactions included acne (10.7%, bacterial vaginitis (10.7%) and depression or mood change (9.6%). Table 4 presents the most common adverse reactions:

Table 4: Adverse Reactions ≥ 1.9% in phase 3 trial L102*

Preferred Term	% Subjects (n=1,751)
Acne	10.7
Bacterial Vaginitis	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

*Modified from Table 30 in the Medical Officer's review dated February 23, 2015.

After review of the adverse reaction data, the Medical Officer concluded in his February 2015 review that, "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.".

The CDTL concurred with the Medical Officer's conclusions on the adverse reaction profile and added in her February 25, 2015 review that, "Many of the adverse reactions are common complaints in reproductive aged women, and in the absence of a placebo-control, it is difficult to determine if they are drug-related. However, a number of them are known progestin-associated AEs (acne, breast symptoms, mood changes, nausea, headache, etc.) Ovarian cysts and bleeding AEs are likely related to the IUS. Overall, the rates and types of AEs are not unusual."

Comment: I concur with the Medical Officer and CDTL that there are no unexpected or unique safety signals that were identified in the adverse event profile for Liletta.

The Medical Officer also evaluated vital sign and data on body weight changes and did not identify a safety signal or trend for Liletta.

Events of Specific Interest to Liletta

1. Ease of removal is a specific concern when an IUS, such as Liletta, is placed. An analysis evaluated removal of the IUS (by pulling on the IUS string) at study discontinuation. Difficulty with removal was noted in 15 subjects of the 326 subjects from the phase 3 trial L102 who had data from the investigator on their discontinuation (15/326 = 4.6%). Not all data on discontinuation is available as subjects may have had their IUDs removed by a non-study provider. The following difficulties with removal were reported:
   - Required alligator forceps – 4 subjects
   - Required use of other instrumentation – 3 subjects
   - Required local anesthesia – 3 subjects
   - Required ultrasound guidance – 2 subjects
   - Removed in the operating room – 2 subjects
   - Consent withdrawn - 1 subjects

2. Ovarian cysts are a specific concern based on safety profiles of other approved LNG IUS devices. Ultrasounds were not routinely done in phase 3 trial L102. The safety data on ovarian cysts is solely based on symptomatic ovarian cysts. In the safety database for Liletta, a total of 47 subjects (47/1,751 [2.7%]) had a reported adverse event of an ovarian cyst. However, only 5 subjects (0.3%) discontinued because of an ovarian cyst. In his February 2015 review, the Medical Officer did not concluded that these events were unexpected or represented a significant clinical concern.

Comment: The Medical Officer reviewed the ease of removal data and data on ovarian cysts and did not identify a safety signal or trend. I concur that there is no safety signal or new safety trend from this data. However, the rate of ovarian cysts identified in the phase 3 trial will be included in labeling as these cysts can result in pelvic pain, abdominal pain or dyspareunia that may result in further medical evaluation and/or discontinuation of Liletta.

Supportive Safety Data:

Two phase 1 studies were submitted to support use of redesigned inserters for Liletta. These phase 1 studies include:

- Study L103: A phase 1 study in 50 women to evaluate the safety (b) (4) single handed inserter (SHI-001). Eligible subjects (18 to 45 years of age), after informed consent and screening was performed, had Liletta placed in their uterus using the SHI-001 inserter. 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. Follow-up was conducted as needed and no control or comparison group was utilized. Successful IUS placement occurred in 48 of 50 (96%) of subjects. IUS placement was classified as "easy" in 44 of 50 subjects. IUS placement was unsuccessful in 2 of 50 subjects (4%). A total of 12 subjects (24%) had treatment emergent adverse events and no deaths or SAEs were reported. The only adverse event reported for more than 1 subjects was metrorrhagia in 5 subjects, although 9 subjects (18%) had adverse events related to IUS placement (back pain, syncope, bleeding from tenaculum site, sensation of low back pain and dysmenorrhea).

- Study L104: A phase 1 study in 100 women (57% nulliparous) who had insertion of Liletta attempted to assess the safety and performance of the to-be-marketed two-handed inserter (THI-002). Eligible subjects (18 to 45 years of age), after informed consent and screening was performed, had Liletta placed in their uterus using the THI-002 inserter. Liletta was removed approximately 24 hours after IUS placement if, in the opinion of the investigator, it was clinically safe to do so. A Visual Analog Scale for pain was obtained before the IUS was removed. Follow-up was conducted as needed and no control or comparison group was enrolled. IUS placement was classified as "easy" in 55 of 100 subjects (55%), neutral in 24 subjects (24 of 100 [24%]) and "difficult" in 19 subjects (19 of 100 [19%]). IUS removal occurred in 98 subjects who had a removal visit, one subject had the IUS removed in the emergency room and one had an unsuccessful placement. A total of 41 subjects had treatment emergent adverse events (41%) and no deaths were reported. One SAE of gastroenteritis occurred that was not considered by the clinical team or the Applicant to be related to IUS use. Of the adverse events reported, a total of 31 were considered adverse reactions related to the IUS with the most common being abdominal pain (20 subjects), vaginal bleeding (17 subjects), pelvic discomfort (4 subjects) and uterine pain (4 subjects). Parous women reported more IUS-related AEs compared to nulliparous (37% vs. 26%) with vaginal bleeding (30% vs 7%) and abdominal pain (26% vs 16%) being the most common in that sub-group.

Comment: In his February 2015 review, the Medical Officer noted that the two Phase 1 studies that evaluated the two different inserters (SHI-001 and THI-002) did not demonstrate any unexpected adverse events or safety trends. However, there were some findings with the THI-002 to-be-marketed inserter that were concerning because of their relationships to the inserter and occurrence in several subjects:

- *Difficulty passing the inserter due to kinking*
- *IUS pulled out with removal of the inserter*
- *Difficulty loading the inserter*
- *Failure to place the IUS on the first visit*

After reviewing the adverse events and notable inserter issues that were identified with the THI-002 inserter and because this inserter was not used in the phase 3 trial, a

postmarketing commitment study will be obtained to further evaluate the performance of the inserter in the intended patient population.

A European study evaluating the same IUS as Liletta (under the tradename Levosert-20) for the indication of menorrhagia was submitted as additional supportive safety data for Liletta. This study evaluated 141 women who used Liletta and 139 subjects who used Mirena. In his February 2015 review, the clinical reviewer stated that after review, "The safety data from this menorrhagia study do not raise any safety concerns or new signals."

Comment: I concur with the Medical Officer that there are no concerning safety signals for Liletta from the European study in patients with menorrhagia. As this population is clinically different from the intended population in the US, this data will not be included in labeling.

Other Significant Safety Issues:

The clinical review team identified specific safety issues relevant to a LNG IUS based on the known safety profiles of currently approved LNG IUS products (Mirena [NDA 021-225] and Skyla [NDA 203-159]). The safety review included evaluation of ectopic pregnancies, pelvic inflammatory disease and endometritis, uterine perforation and expulsion of the IUS. These issues along with a request for any postmarketing data were discussed with the Applicant. An overview of the specific safety issues included:

1. Ectopic Pregnancy:

The risk of ectopic pregnancy (pregnancy diagnosed outside of the uterine cavity) has been associated with use of approved LNG IUS products. Although IUS prevent both intrauterine and extrauterine pregnancies, the proportion of pregnancies that occur with use of an IUS are more likely to be ectopic, although the actual risk of an ectopic pregnancy is very low. In trial L102, there were 5 ectopic pregnancies in the Liletta arm (0.2%). One ectopic pregnancy occurred in Year 1, three ectopics in Year 2 and one ectopic in Year 4 (not included in the efficacy analyses for the requested three year indication). Two ectopic pregnancies occurred in nulliparous subjects and three in parous subjects.

Based on the updated exposure and pregnancy data through December 19, 2014, the Applicant calculated the overall ectopic pregnancy rate in the safety population as 0.12 per 100 women-years of use.

Comment: From a clinical perspective, I agree with the Applicant, Medical Officer and CDTL that the risk of overall ectopic pregnancies is low, and there is no unexpected safety signal concerning the risk of ectopic pregnancy for this product. However, the occurrence of an ectopic pregnancy can be a life-threatening adverse event. Therefore, I also concur that this risk should be included in labeling of Liletta as it has been for other approved IUS products in the WARNINGS AND PRECAUTIONS section.

2. Pelvic Inflammatory Disease and Endometritis:

Pelvic inflammatory disease (PID) was diagnosed based on standard criteria that included tenderness on pelvic examination, lower abdominal pain and at least two of the following criteria:

- Purulent or abnormal vaginal discharge
- Increased C-reactive protein (>30 mg/L)
- Increased temperature (>38^{o} C)
- Typical findings at laparoscopy (if other clinical evidence was controversial)
- Evidence of Chlamydia or Gonorrhea in the cervical canal

Other intrauterine infections that did not meet the criteria for PID were classified as "endometritis". Of note, the investigator's clinical assessment was required for the final diagnosis, so not all suspected cases of PID may have been included as a case of PID in the safety dataset. The Medical Officer reviewed the 10 cases of intrauterine infections (PID and endometritis), and provided the following summary in his February 2015 review:

"A total of 10 (0.6%) Liletta subjects reported intrauterine infection. 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 the 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%) of 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."

The Medical Officer concluded that the occurrence of intrauterine infection with Liletta was approximately 0.57%.

Comment: I concur with the Medical Officer that the number of cases of endometritis/PID reported in phase 3 trial L102 do not appear excessive based on the known risk with other approved IUS products. I also concur that this serious risk should be included in labeling in the WARNINGS AND PRECAUTIONS section.

3. Perforation of the IUS:

A total of 3 Liletta subjects had a uterine perforation in the phase 3 trial which results in a rate of 0.001% (3/1,751), all in the age 16-35 years group with use of the THI-001 inserter. One of these perforations was due to sounding of the uterus prior to IUS placement (Subject 125-0046), and was not associated with the inserter.

Comment: The rarity of perforation with Liletta, particularly with the two-handed inserter (THI-001) is reassuring and does not appear clinically to be different from other approved IUS products. It is expected that the new two-handed inserter (THI-002), which was modified to be easier to use, will decrease the risk of perforation. However, as this risk can lead to life-threatening adverse events including intestinal perforation, intestinal obstruction, abscesses and erosion of adjacent viscera, this adverse reaction will be included in labeling in the WARNINGS AND PRECAUTIONS section. In addition, this risk will be captured in the postmarketing period in a commitment and data from that study may be included in future labeling revisions.

4. Expulsion of the IUS:

Total expulsion was defined as when the IUS was observed in the vagina, not shown in the uterus by ultrasound, or if the woman confirmed expulsion. Perforation was to be excluded in all cases. Partial expulsion was defined as when the IUS was visualized in the cervical canal on gynecologic exam or ultrasound. Partially expelled IUS were removed and women discontinued from the trial.

Based on the original data along with data from the 120-day safety update, a total of 59 cases were identified over 3 years, which results in a rate of 3.4% (59/1,751). The Applicant and primary clinical reviewer noted that this rate was similar to rates of expulsion in other approved IUS products in the US (e.g. Skyla – 3.2%). Of note, an additional 3 cases were identified in Year 4 of use, resulting in a rate of 3.5% (62/1751).

Comment: I agree with the Applicant and the clinical review team that the rate of expulsion appears to be consistent with other approved IUS products in the US. As expulsion results in total loss of the contraceptive efficacy, this adverse

reaction will be labeled using all safety data submitted (which including available data from subjects in Year 4 of trial L102) in the WARNINGS AND PRECAUTIONS section. Data on expulsion of Liletta will also be captured through a postmarketing commitment study and the data may be included in future labeling revisions.

5. Postmarketing data summary:

No postmarketing safety data are available for Liletta because it had not been approved anywhere at the time of submission. The European IUS approved for menorrhagia as Levosert is owned by another company, and has been marketed in two European countries since spring 2014. The Applicant provided the following post-marketing AE reports from Europe that were received; two expulsion reports, one uterine infection report, two placement failures of the IUS and one report of difficult placement. Several of the postmarketing reports were associated with off-label use.

Comment: Hypersensitivity to the IUS and device breakage have been reported during the postmarketing period for other IUS products. These postmarketing adverse reactions will be included in labeling.

Safety summary:

The clinical review team determined that the safety database for Liletta was adequate to characterize the safety profile of Liletta. The safety findings are acceptable and support approval of Liletta for prevention of pregnancy for up to 3 years of use. The relevant safety issues for Liletta were identified and have been sufficiently addressed in labeling, including the risk of ectopic pregnancy, pelvic inflammatory disease and endometritis, perforation and expulsion. Other potential risks associated with LNG-releasing IUS products, including breast cancer and sepsis, were also incorporated in labeling.

In summary, the Medical Officer concluded the following on the safety of Liletta in his review dated February 23, 2015, "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."

The Cross-Discipline Team Leader (CDTL) concurred with the primary Medical Officer's assessment of the safety issues identified with Liletta in her CDTL review dated February 25, 2015 and stated that, "Overall, the safety profile of Liletta appears acceptable to support approval for prevention of pregnancy for up to three years in women (b) (4) ."

I concur with the recommendations of the primary Medical Officer and CDTL that there are no remaining safety concerns that preclude approval of this NDA.

9. Advisory Committee Meeting

The first intrauterine system containing levonorgestrel, (Mirena) was initially approved under NDA 21-225 in the US on December 6, 2000 for prevention of pregnancy. Since then, a second IUS with levonorgestrel (Skyla – NDA 203159) has been approved in the US. Both of these IUS are available for use in current clinical practice. Safety issues associated with these levonorgestrel intrauterine systems are known and can be adequately labeled. In addition, no new safety concerns were identified for Liletta. Therefore, no Advisory Committee was convened.

10. Pediatrics

The Division recommended a full waiver of pediatric studies in pre-menarchal girls because they are not at risk of becoming pregnant and use of this product before menarche is not recommended. In post-menarchal adolescents, the Applicant fulfilled the PREA requirement by extrapolation of adult data to this age group.

11. Other Relevant Regulatory Issues

Division of Medical Policy Programs (DMPP):

DMPP reviewed the Patient Package Insert (PPI) in conjunction with the Office of Prescription Drug Promotion. Both DMPP and OPDP found the PPI to be acceptable with recommended changes, as stated in their review dated January 29, 2015. These recommendations were sent to the Applicant and were implemented in final PPI labeling.

Office of Prescription Drug Promotion (OPDP):

OPDP reviewed the Patient Package Insert (PPI) in conjunction with the DMPP. Both OPDP and DMPP found the PPI to be acceptable with recommended changes contained in their review dated January 29, 2015. These recommendations were sent to the Applicant and were implemented in final PPI labeling.

On January 30, 2015, OPDP reviewed the proposed patient insert (PI) based on a substantially complete PI dated December 26, 2014. Also on January 30, 2015 OPDP provided a separate review of carton/container labeling. Comments from OPDP on the PI and carton/container labeling were sent to the Applicant and implemented in final labeling.

Office of Scientific Investigations (OSI):

OSI conducted inspections of two clinical sites (Drs. Eisenberg and Westhoff) that were the highest enrolling sites in the pivotal phase 3 trial and that had not undergone previous

inspections. The Clinical Inspection Summary stated that, "The clinical sites of Drs. Eisenberg and Westhoff were inspected in support of this NDA. Dr. Eisenberg was not issued a Form FDA 483, and the final classification of this inspection was No Action Indicated (NAI). Dr. Westhoff was issued a Form FDA 483; however, the deficiencies noted were isolated and would not appear to have adversely affected safety or efficacy considerations, and the final classification of this inspection was Voluntary Action Indicated (VAI). The data generated by these clinical sites appear adequate in support of the respective indication." (See OSI Clinical Inspection Summary dated January 7, 2015 and NAI letter to Dr. Westhoff finalized on December 15, 2014 and VAI letter to Dr. Eisenberg finalized on January 7, 2015).

Comment: I concur that there are no outstanding issues from the OSI perspective that require additional investigation or response.

Division of Medication Error Prevention and Analysis (DMEPA):

The DMEPA review team evaluated the pouch label, carton insert, patient booklet cover labeling, patient reminder card and patient reminder sticker. In the DMEPA review dated November 5, 2014, the team concluded, "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, DMEPA's recommendations were conveyed to the Applicant. These recommendations were implemented in final labeling for Liletta.

The DMEPA review team also assessed the proposed tradename "Liletta" and found it acceptable.

Financial Disclosures**:**

The clinical review team did not identify any issues of serious concern related to financial disclosures for the phase 3 study (See Medical Officer review dated February 23, 2015).

CDRH review of the IUS inserter:

The CDRH biomedical engineers reviewed functionality of the drug-delivery device (inserter), the human factors considerations, and other aspects of the device. The phase 3 study used two different inserters: a two-handed inserter referred to as THI-001 and a single handed inserter (SHI-001). (b) (4) the firm developed a modified two-handed inserter (THI-002) for commercial use. During the pre-NDA interactions, the Applicant was notified that a clinical study would be needed with the modified inserter (THI-002) for approval. The Applicant conducted a phase 1 study (M360-L104) at 6 sites with 100 women receiving the Liletta IUS using the THI-002 inserter to support safe use of the new inserter. CDRH was consulted on the following:

- Functionality of the THI-002 inserter – reviewed by Veronica Price, Biomedical Engineer Human Factors Review – reviewed by Quynh Nguyen, Biomedical Engineer
- Information pertaining to magnetic resonance (MR) labeling, recommended by CDRH for all "implanted devices" –reviewed by Terry Woods, Ph.D.

- CDRH Office of Compliance inspection – a consult was requested to evaluate the medical device constituents of the combination product (IUS + inserter) and determine if an inspection of the manufacturing facilities would be required. Inspection of the manufacturing site, Odyssea Pharma S.A., was recommended, and this was conducted on August 18-22, 2014.

Functionality of the inserter: Dr. Price reviewed the design, shelf-life, design verification/validation testing and clinical testing of the THI-002 (the to-be-marketed) inserter. She identified certain deficiencies related to shelf life and design verification/validation testing and requested the Applicant provide a response. Upon the Applicant's response, she provided the following conclusion in her review dated January 23, 2015, "All of the deficiencies identified in my original review have been resolved. I have no outstanding issues on the THI-002 inserter."

Human Factors: Dr. Nguyen reviewed the user's Failure Modes and Effects Analysis (FMEA) and the Applicant's rationale for not conducting a human factors study with the THI-002 inserter. She made the following conclusions in her review dated October 15, 2014, "The Sponsor has submitted a use Failure Modes and Effect Analysis (uFMEA) along with a rationale for why they do not believe a human factors validation testing is necessary on 9/10/2014 in responding to FDA Information Request email. The uFMEA identified some potential patient effects associated with the use of the device that are concerning the human factors reviewer such as hemorrhage, perforation, infection, etc.

However, the Sponsor reported that a clinical study report (M360-L104) was submitted as SN0007 to the NDA as 120-day safety update.
The Sponsor rationalized that this study confirmed the results of the uFMEA whereby no new risks or unacceptable risk levels were identified, and it also provided evidence that the medical device, as designed, can be used safely and effectively under the actual use conditions in accordance with the instructions for use. Because the actual clinical study supersedes CDRH HFPMET's simulated human factors study requirement, and CDRH HFPMET does not have the expertise to review the clinical study report, this human factors reviewer defers to the medical officer on the team to determine the acceptability of the clinical study results. If it is believed that the clinical study results support the Sponsor's conclusion in terms of no new/unacceptable risks were identified and the device can be used safely and effectively under actual use conditions, then this reviewer will accept the Sponsor's rationale for why a human factors validation study is not needed."

MR Testing and Labeling: The Applicant confirmed that Liletta contains no metal determined to be "MRI-conditional." Terry Woods, Ph.D., reviewed the submitted information about MR safety testing and labeling. Dr. Woods determined that because Liletta is composed entirely of polymer materials, and contains no metal, it may be labeled as MR Safe without any testing. A minor labeling revision was conveyed to the Applicant and accepted by the Applicant.

Device Inspection: An additional consult request was submitted to the CDRH Office of Compliance to evaluate the medical device constituents of the combination product and determine if an inspection of the manufacturing facilities would be required. A determination was made by the CDRH Office of Compliance that information provided to demonstrate compliance with applicable provisions of the Medical Device Quality System Regulation (21 CFR 820) was acceptable along with inspection of Odyssea Pharma S.A. The reviewer, Bleta Vuniqi, stated that, "The Office of Compliance at CDRH has completed the evaluation of application NDA 06629. Sufficient information was provided by the sponsor to demonstrate compliance with applicable provisions of the Medical Device Quality System Regulation (21 CFR 820). NDA 206629 application was determined to be acceptable. Additionally, the inspection of Odyssea Pharma S.A. (FEI # 3007966308) has been conducted and is deemed acceptable. The Office of Compliance at CDRH recommends approvability of NDA 206629 application."

Comment: I concur with the CDRH reviewers that there are no outstanding concerns with the THI-002 inserter. In addition, the study results from L104 with the to-be-marketed THI-002 inserter were sufficient from the clinical perspective to determine that the inserter device can be used safely without an additional human factors validation study. For more details on the clinical review of the THI-002 inserter and its adequacy, see Section 8 of this review.

12. Labeling

Labeling discussions are complete. Labeling for Liletta was acceptable to the review teams. Labeling was also evaluated by the following groups:

- Office of Medical Policy Programs (DMPP) reviewed the Patient Package Insert jointly with the Office of Prescription Drug Promotion and their recommendations on the PPI were considered during labeling negotiations with the Applicant.
- Office of Prescription Drug Promotion (OPDP) reviewed the Package Insert and Carton/Container labeling and their recommendations were considered during labeling negotiations with the Applicant.
- The Division of Pediatric and Maternal Health (DPMH) reviewed the labeling regarding use in pregnant and lactating women. On February 20, 2015, the DMPH reviewer provided recommendations on sections 8.1, 8.2 and 17.1 of physician labeling. These recommendations were implemented.

An edited version of the label was sent to the Applicant. No additional labeling review by SEALD was required.

13. Decision/Action/Risk Benefit Assessment

Decision:

I agree with the Cross-Discipline Team Leader, Medical Officer, and the Clinical Pharmacology, Pharmacology/Toxicology, CMC, Statistical review teams along with CDRH consultants that the Liletta (levonorgestrel-releasing intrauterine system) application should receive an Approval action.

Risk Benefit Assessment:

Efficacy and safety data from the one phase 3 trial demonstrated that Liletta was effective and safe for prevention of pregnancy for 3 years of use. Supportive safety data was provided from two phase 1 studies that evaluated two different inserters (Studies L103 and L104) as well as a European trial in women with menorrhagia (Levosert-20) using an IUS (b) (4) Liletta under the tradename Levosert-20.

Two different inserters (THI-001 and SHI-001) were used at various times in the phase 3 trials. The initial inserter was a two-handed model (THI-001). Due to patient discomfort and difficult insertions, the trial was halted (b) (4) The Applicant assessed the safety (b) (4) of the SHI-001 inserter in 50 women (through Study L103) prior to restarting the phase 3 trial with the SHI-001 inserter. (b) (4) the Applicant opted to market Liletta with a modified two-handed inserter, THI-002, which was a redesign of the THI-001 inserter used in the phase 3 trial. The Applicant evaluated the safety and performance of the inserter THI-002 in 100 healthy female subjects age 18-45. Although the clinical team, in consultation with CDRH device reviewers, determined that the safety and performance of the THI-002 inserter with Liletta was acceptable for approval, the team recommended that additional long-term safety data with the redesigned THI-002 inserter be collected in a postmarketing commitment study (See Postmarketing Commitment section below)

No significant unexpected safety concerns were identified in the safety database of Liletta that preclude approval by the clinical reviewers or the Center for Devices and Radiologic Health (CDRH) reviewers. In addition, no device-related issues were identified by the CDRH review teams. The size and scope of the safety database were sufficient to adequately characterize the safety profile of Liletta. Specific safety concerns identified included risks of ectopic pregnancy, pelvic inflammatory disease, perforation and expulsion; these risks are known to other approved intrauterine systems in the US. These risks and other adverse reactions identified during the phase 3 trial have been adequately addressed in labeling.

In my opinion, the benefit/risk for Liletta is favorable and I recommend that Liletta be approved for the prevention of pregnancy for 3 years of use.

Post-Marketing Requirement/Commitment and Risk Evaluation and Mitigation Strategies (REMS):

- The review teams determined that a REMS was not necessary for this product.
- The review teams also determined that a postmarketing commitment (PMC) study (#2874-1) is warranted to further evaluate use of the to-be-marketed inserter, which was not studied in the phase 3 trial L102. The Applicant agreed to conduct this PMC study as follows:
    - A descriptive observational cohort study to evaluate performance of the THI-002 inserter in women receiving Liletta. The study cohort will include a minimum of 1,000 women who receive Liletta using the THI-002 inserter in a variety of clinical settings. The study should enroll representative proportions of nulliparous users and obese women to reflect the overall user population for the labeled indication. The enrolled subjects should be followed for a minimum of three months after insertion to monitor for expulsion, perforation and infection because these adverse events are more common during this time period and may be related to the inserter or the insertion process. 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. IUS removal data are not of primary importance and do not need to be obtained unless the IUS was removed specifically due to an insertion-related adverse event. The following milestones were agreed to by the Agency and the Applicant:
        - Final study protocol: 2/16
        - Study completion date: 2/18
        - Final study report: 2/19

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

/s/

AUDREY L GASSMAN
02/26/2015