

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

206229Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

OFFICE OF CLINICAL PHARMACOLOGY REVIEW ADDENDUM

| | | |
|---------------------------------|--|--|
| NDA 206229 | Submission Dates | 4/30/14, 5/22/14, 5/30/14, 8/29/14, 9/10/14, 12/16/14, 1/26/15, 2/18/15, 2/19/15 |
| Brand Name | Liletta™ | |
| Generic Name | levonorgestrel-releasing intrauterine system | |
| Reviewer | Li Li, PhD | |
| Team Leader | Myong Jin Kim, PharmD | |
| OCP Division | Division of Clinical Pharmacology 3 | |
| OND Division | Division of Bone, Reproductive and Urologic Products | |
| Sponsor | Medicines 360 Inc. | |
| Submission Type | Original | |
| Formulation; Strengths; Regimen | Intrauterine system containing 52 mg of levonorgestrel with an initial release rate of 18.6 µg/day | |
| Proposed Indication | Prevention of pregnancy for up to 3 years | |

1 Executive Summary

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.

1.1 Recommendation

The Division of Clinical Pharmacology-3, Office of Clinical Pharmacology finds the NDA 206229 acceptable.

3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

LI LI
02/24/2015

MYONG JIN KIM
02/24/2015

| BIOPHARMACEUTICS REVIEW | | | |
|--|--|--|-----------------|
| Office of New Drug Products | | | |
| Application No.: | NDA 206229 | Primary Reviewer: Kelly M. Kitchens, Ph.D. | |
| Submission Date: | April 17, 2014 | | |
| Division: | Division of Bone, Reproductive, and Urologic Products | Secondary Reviewer: Tapash Ghosh, Ph.D. | |
| Applicant: | Medicines360 | | |
| Trade Name: | Liletta® | Date Assigned: | May 14, 2014 |
| Established Name: | Levonorgestrel Releasing Intrauterine System | Date of Review: | January 8, 2015 |
| Indication: | Indicated for intrauterine contraception (b)(4) | Type of Submission: NDA 505(b)(2) | |
| Formulation/ strengths | Intrauterine Device/52 mg | | |
| Route of Administration | Intrauterine | | |
| Type of Review: | In Vitro Drug Release Method and Acceptance Criteria; In Vivo Drug Release | | |
| <u>SUMMARY:</u> | | | |
| <p>Background: On May 14, 2014, Medicines360 submitted NDA 206229 for Liletta® (levonorgestrel releasing intrauterine system). Liletta is a levonorgestrel-releasing IUS designed for intrauterine use following insertion by a trained healthcare professional. Levonorgestrel is a second-generation synthetic progestogen whose pharmacological effects are similar to those of the natural hormone progesterone. Liletta is a highly effective form of long-acting reversible contraceptive that is indicated for prevention of pregnancy for up to 3 years (b)(4). The IUS itself contains 52 mg of levonorgestrel (LNG) that is initially released at a rate of 18.6 µg/day. This rate decreases progressively to approximately 16.3 µg/day at 1 year, 14.3 µg/day at 2 years, and 12.6 µg/day at 3 years after insertion.</p> <p>Submission: The NDA submission includes drug release method development and the proposed drug release acceptance criteria.</p> <p>Review: The Biopharmaceutics review is focused on the evaluation of the drug release method development and drug release data for the proposed dissolution specification value.</p> | | | |

RECOMMENDATION:

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

Signature

Kelly M.
Kitchens -S

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Date: 2015.01.16 11:37:04 -05'00'

Kelly M. Kitchens, Ph.D.
Primary Biopharmaceutics Reviewer
Office of New Drug Products

Signature

Tapash K.
Ghosh -S

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Tapash Ghosh, Ph.D.
Secondary Biopharmaceutics Reviewer
Office of New Drug Products

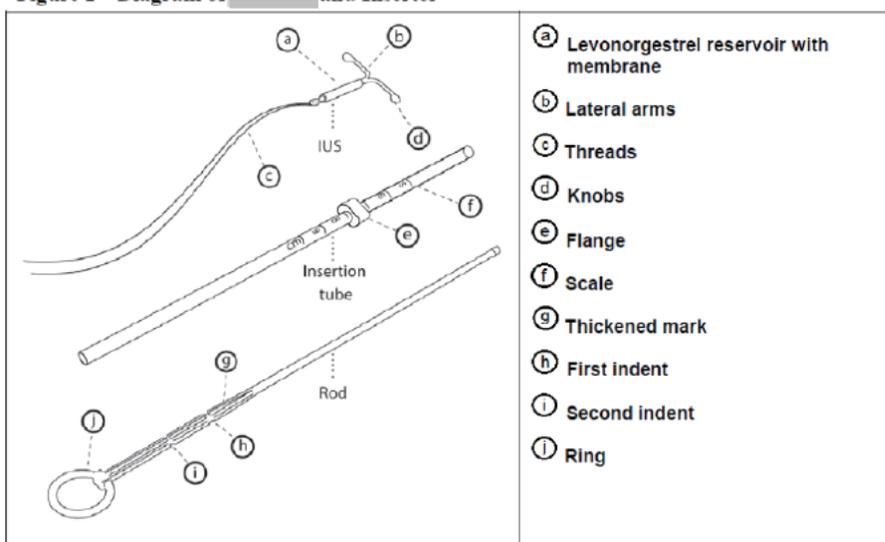
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BIOPHARMACEUTICS ASSESSMENT

Drug Product:

- Liletta is a levonorgestrel-releasing IUS designed for intrauterine use following insertion by a trained healthcare professional. Levonorgestrel is a second-generation synthetic progestogen whose pharmacological effects are similar to those of the natural hormone progesterone. As a 19-nortestosterone derivative progestin, levonorgestrel has potent progestational and anti-estrogenic effects. The chemical name of levonorgestrel is (-)-13-Ethyl-17-hydroxy-18,19-dinor-17 α -pregn-4-en-20-yn-3-one. The empirical formula is C₂₁H₂₈O₂ and the molecular weight is 312.4.
- Liletta contains 52 mg of levonorgestrel combined with polydimethylsiloxane (PDMS) to form a silicone (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 BaSO₄ for radio-opacity. A polypropylene monofilament thread is attached to an eyelet at the base of the T-frame for IUS removal. A schematic of the complete system is shown in the following figure:

Figure 2 Diagram of (b) (4) and Inserter



In Vitro Release Method Development:

The Applicant developed the following in vitro release method for Liletta to be used as a quality control (QC) release test:

| Apparatus | Agitation Speed | Medium | Volume | Acceptance Criteria |
|----------------------------|-----------------|---|---|---|
| (b) (4) shaking water bath | 140 rpm | Water (pH 5.5-7.5) containing methyl- and propyl-parahydroxybenzoate as preservatives (also referred to as Aqua Conservans) | 250 ml (glass bottle containing medium) | Day 1: (b) (4) g/day Day 3: (b) (4) g/day Day 14: (b) (4) μ g/day |

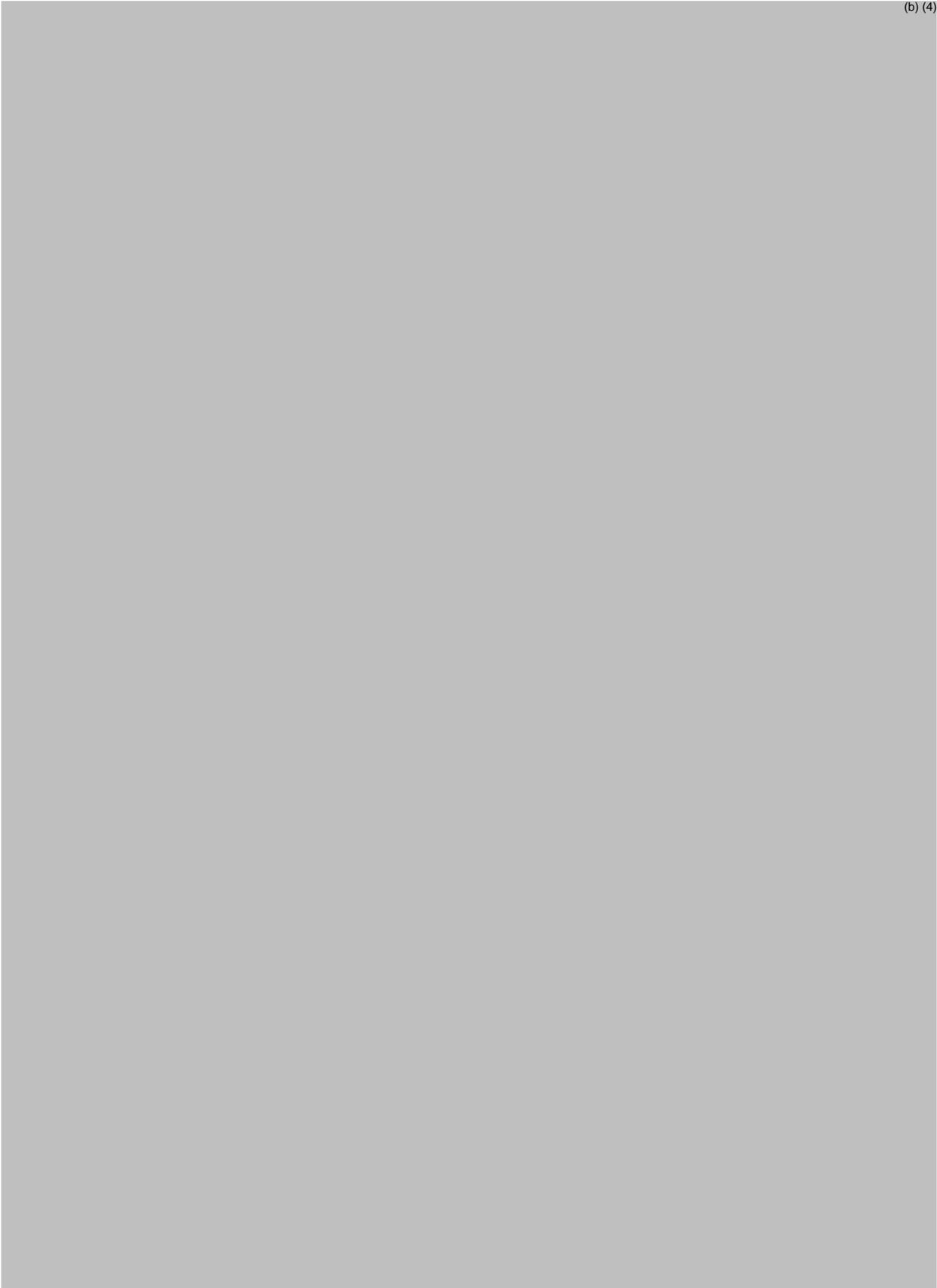
| Parameters | Data |
|--|--|
| Source of data | Levonorgestrel Intrauterine System (LNG20 IUS) – In Vitro Release Rate Test: Method Development Report REP-00049 |
| Apparatus | Shaking water bath was selected for the following reasons: <ul style="list-style-type: none"> • Maintain consistent temperatures • Maintain consistent agitation speeds • Water bath tray was able to hold vessels of the right size and shape • Agitation rate could be adjusted to deliver acceptable release • Water bath and bottles would allow testing over extended periods, with no evaporative loss • Incubator shaker is the apparatus used in the approved drug release method for another vaginal ring product |
| Container | A 250 mL amber bottle was selected as the container because release rates from 250 mL and 300 mL containers were similar. |
| Diffusion Medium | Water containing methyl- and propyl-parahydroxybenzoate (Aqua Conservans) was selected as the diffusion medium for the following reasons: <ul style="list-style-type: none"> • Solubility of LNG was similar over the pH range (1.20 µg/mL – 1.08 µg/mL for pH 2-10 20 mM phosphate buffer) • 0.1% parabens (methyl- and propyl-parahydroxybenzoates) were used as an anti-microbial • LNG release is similar in water, phosphate buffer pH 7.4, and phosphate buffer pH 5.5 over 78 days (11 weeks) • Sink conditions are met |
| Temperature | <ul style="list-style-type: none"> • The temperature that the test is performed (37°C) was chosen because it corresponds to physiological temperature, and is consistent with USP <711> • The method requires the temperature to be controlled at 37°C ± 0.5°C, because a robustness study demonstrated that LNG release changes with temperature change |
| Agitation Rate | <ul style="list-style-type: none"> • The agitation speed of 140 rpm was selected based on previous experience at the testing laboratory • Agitation set to 140 rpm closely reproduced the desired in vivo release rate of (b) (4) µg/day |
| Discriminating Ability: Membrane Thickness | <ul style="list-style-type: none"> • The LNG IUS specification for membrane thickness is (b) (4). LNG release was measured from IUSs manufactured with membrane thickness of (b) (4). • Although the mean values of LNG release from the different IUS products suggest that the release method is able to discriminate between different IUS membrane thicknesses, the Applicant did not report the variability of LNG release; therefore, this Reviewer cannot agree to the claim the method is discriminating to IUS membrane thickness. |
| Discriminating Ability: Membrane Damage | <ul style="list-style-type: none"> • IUS membranes were intentionally damaged by a (b) (4) incision made into the membrane. LNG release was measured from IUSs with damaged membranes and intact IUS membranes. • Although the mean values of LNG release from the different IUS products suggest that the release method is able to discriminate between different IUS membranes that are intact or damaged, the Applicant did not report the variability of LNG release; therefore, this Reviewer cannot agree to the claim the method is discriminating to IUS membrane damage. |

Reviewer's comments on drug release method development and validation:

- The in vitro release method is acceptable.



(b) (4)



Reviewer's comments on drug release acceptance criteria:

- The Applicant's approach for establishing acceptance criteria is acceptable, and the batches tested meet the proposed drug release acceptance criteria; however, the Applicant did not provide any drug release data at time 0 (i.e. before the batches are placed at long-term stability conditions). Therefore, the following Information Request (IR) was communicated to the Applicant on November 5, 2014:

Provide in vitro drug release data at time 0 (i.e. before the batches are placed at long-term stability conditions) for as many of your clinical and stability batches as possible using your proposed in vitro release method. Ensure that you include the complete release data (i.e. individual, mean, standard deviation, and profiles) for each batch tested.

We request this information by COB December 15, 2014.

On November 18, 2014, the Applicant provided the following response to the IR:

The complete in vitro drug release data at time 0 are provided in Appendix 1 for all of the clinical and stability batches submitted to support the NDA. This data includes the individual, mean, standard deviation and profiles for each batch tested.

NOTE: The day 1 time point was added during development, and therefore there is no day 1 data at time 0 for the earlier batches 09-009, 09-012, 09-013, and CT-11I09.

(b) (4)





The proposed drug release acceptance criteria are acceptable.

In Vivo Release Rate:

- A summary of the Phase 3 study (Report No. PRDR-021, “M360-L102 Three Year *Ex Vivo* Release Rate Estimate”) is described as follows:

Purpose: Estimate the *in vivo* release rate of levonorgestrel from LNG20 (Liletta) over the duration of the Applicant’s pivotal phase 3 clinical trial (M360-L102).

Sampling: 10 randomly selected samples were analyzed at lot release, and LNG content analysis was performed on 6 or more removed or expelled samples in each 90 day interval thereafter through 2.5 years, and 6 samples between 2.5 – 3 years.

Sample storage: [redacted] (b) (4)

LNG Content Analysis:

- The measured LNG content of 74 samples was used to estimate the average *in vivo* drug release rate during the time the samples were implanted.

- The drug content of each sample analyzed was plotted vs. the duration of exposure and plotted. The exponential best fit regression was used to calculate the average rate of change of system content vs. time based on a mono-exponential decay content model.

Bioanalytical analysis: See the Clinical Pharmacology review by Dr. Hyunjin Kim for the acceptability of bioanalytical results.

Results:

- The initial average release rate of the IUS is 18.6 µg/day, and decreased on average from 52.0 mg to 35.1 mg over 3 years, or decreased from 18.6 µg/day to 12.6 µg/day. The estimated release rate was determined by residual drug content analysis of 74 samples that were removed or expelled over the course of the Phase 3 study.
- The residual content versus time of intrauterine exposure for all samples and best fit exponential curve is shown in the following figure:

Figure 2 Levonorgestrel Content of Levosert IUSs Removed or Expelled versus Exposure Duration

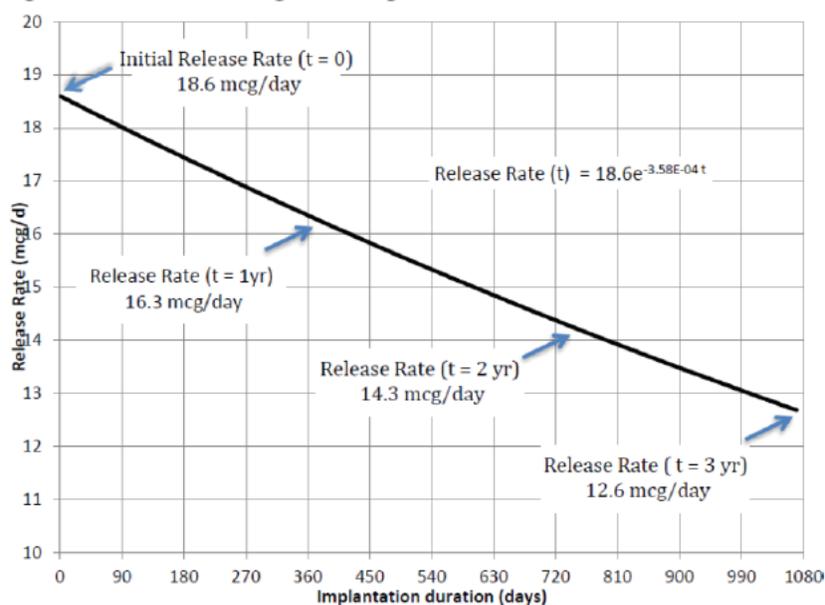


Source: M360-L102 Appendix 16.2.5, "M360-L102 Three Year Ex Vivo Release Rate Estimate"

- The intercept of the regression (content at time = 0) was set to 52 mg, which was the average drug content of the materials used to supply the clinical trial as determined during release testing of lot number 09-013. The best fit exponential decay constant (k) of the data was (b) (4). The average cumulative release based on the difference between the average initial lot content of 52 mg and the exponential regression curve at 1, 2, and 3 years are approximately (b) (4) respectively.
- The average release rate is the derivative (i.e., the average rate of change) of the content and was estimated by the following equation:

- Therefore, the initial release rate (at time = 0) was determined to be 18.6 µg/day. The estimated average release rate over the proposed 3-year duration of use is shown in the following figure. Based on this equation, the release rates at 1, 2, and 3 years of use were estimated to be 16.3, 14.3, and 12.6 µg/day, respectively. The average release rate over the 3-year duration of the study was 15.6 µg/d as estimated by the mean of the initial and 3-year release rates as calculated by the equation above.

Figure 3 Estimated Average Levonorgestrel Release Rate Over Time



Source: M360-L102 Appendix 16.2.5, "M360-L102 Three Year Ex Vivo Release Rate Estimate"

Reviewer's comments on in vivo release rate analysis:

- The Applicant used residual LNG analysis to estimate the *in vivo* release rate from 74 samples. Based on the exponential curve constructed from the residual content vs. implantation duration plot, the average initial release rate was estimated to be 18.6 µg/day to a gradual exponential decay to 12.6 µg/day over 3 years.
- The *in vivo* release rate analysis is acceptable.

RECOMMENDATION:

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

Clinical Pharmacology Review

| | |
|--|--|
| NDA Number: | 206229 |
| Related IND Number: | 105836 |
| Submission Dates: | 4/30/14, 5/22/14, 5/30/14, 8/29/14, 9/10/14, 12/16/14 |
| Brand Name: | Liletta™ |
| Generic Name: | levonorgestrel-releasing intrauterine system |
| OCP Reviewer: | Li Li, Ph.D |
| OCP Team Leader: | Myong Jin Kim, Pharm. D |
| OCP Division: | Division of Clinical Pharmacology III |
| OND Division: | Division of Bone, Reproductive and Urologic Products |
| Sponsor: | Medicines 360 Inc. |
| Submission Type: | Original |
| Formulation and Dosing regimen: | Intrauterine system containing 52 mg of levonorgestrel with an initial release rate of 18.6 µg/day |
| Indication: | Prevention of pregnancy for up to 3 years |

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Executive Summary

The Sponsor submitted a New Drug Application (NDA) for Liletta, a levonorgestrel (LNG) intrauterine system (IUS), for the indication of prevention of pregnancy for up to 3 years. Liletta contains 52 mg of LNG. After insertion, the release rate of LNG is 18.6 µg/day initially and decreases to 16.3 µg/day at 1 year, 14.3 µg/day at 2 years, and 12.6 µg/day at 3 years. Other LNG-containing IUS products that are currently available in the US are Mirena® (52 mg) and Skyla® (13.5 mg), and they are indicated for the prevention of pregnancy for up to 5 and 3 years, respectively.

In support of this NDA, the Sponsor conducted a pivotal Phase 3 study (Study M360-L102) to assess the safety and contraceptive efficacy of Liletta. Three additional study reports submitted under this NDA include a Phase 3 study (Study (b) (4)-20) in patients with menorrhagia to provide safety and pharmacokinetic (PK) data, two Phase 1 clinical studies (Study M360-L103 and Study M360-L104) to assess the successful placement of Liletta using inserter SHI-001 and inserter THI-002, respectively, in nulliparous and parous women aged 18 - 45 years.

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).

1.1 Recommendations

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.

1.2 Phase IV Requirement/Commitment

None

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

In vivo Release Rate:

Liletta contains 52 mg of LNG in a cylindrical-shaped reservoir. The reservoir is mounted on the vertical arm of a T-shaped plastic frame and is covered with (b) (4) membrane. The initial *in vivo* release rate is 18.6 µg/day. This rate decreases progressively to approximately 16.3 µg/day at 1 year, 14.3 µg/day at 2 years, and 12.6 µg/day at 3 years after insertion. The average *in vivo* release rate of LNG is approximately 15.6 µg /day over a period of 3 years.

Absorption, Distribution and Elimination

- Absorption

In the pivotal Phase 3 study (Study M360-L102), LNG systemic exposure was determined in a subset of 40 subjects at Day 7 and Months 1, 6, 12, 18, 24, and 30 after Liletta insertion. In addition, LNG plasma concentrations were measured in 243 subjects who completed the Phase 3 study at Month 36. Plasma LNG concentrations following placement of Liletta are shown in **Table 1**.

Table 1 Plasma LNG concentrations (mean ± SD, pg/mL) following Liletta placement

| Initial (Day-7) (N = 40) | Month-1 (N = 40) | Month-6 (N = 36) | Month-12 (N = 33) | Month-18 (N = 30) | Month-24 (N = 29) | Month-30 (N = 9) | Month-36 (N = 243) |
|-----------------------------|---------------------|---------------------|----------------------|----------------------|----------------------|---------------------|-----------------------|
| 252 ± 123 | 216 ± 75 | 195 ± 69 | 170 ± 50 | 149 ± 41 | 147 ± 46 | 135 ± 28 | 135 ± 51 |

The Sponsor did not conduct any studies to characterize the distribution, metabolism and excretion of

LNG. The Sponsor proposes to rely on the literature findings for information on this regard via the 505 (b) (2) regulatory pathway.

- **Distribution**

The apparent volume of distribution of LNG at steady-state following oral administration is reported to be approximately 1.8 L/kg. It is about 98.9% protein-bound, principally to sex hormone binding globulin (SHBG) and, to a lesser extent, serum albumin.

- **Elimination**

- **Metabolism**

Following absorption, LNG is conjugated at the 17 β -OH position to form sulfate conjugates and, to a lesser extent, glucuronide conjugates in serum. Significant amounts of conjugated and unconjugated 3 α , 5 β -tetrahydrolevonorgestrel are also present in serum, along with much smaller amounts of 3 α , 5 β -tetrahydrolevonorgestrel and 16 β -hydroxylevonorgestrel. LNG and its phase I metabolites are excreted primarily as glucuronide conjugates. Metabolic clearance rates may differ among individuals by several-fold, and this may account in part for wide individual variations in LNG concentrations seen in individuals using LNG-containing contraceptive products. In vitro studies have demonstrated that oxidative metabolism of LNG is catalyzed by CYP enzymes, especially CYP3A4.

- **Excretion:**

About 45% of LNG and its metabolites are excreted in the urine and about 32% are excreted in feces, mostly as glucuronide conjugates. The elimination half-life of LNG after a single oral administration is approximately 13.9 \pm 3.2 hours.

Drug Product Formulation & IUS Inserter

Pivotal Phase 3 Formulation vs To-Be-Marketed (TBM) Formulation

Formulation composition of the clinical trial formulation (pivotal Phase 3 study, study M360-L102) and the TBM formulation is the same. There are minor changes in the manufacturing process for the TBM formulation, (b) (4)

(b) (4) The *in vitro* drug release profiles are comparable between the Phase 3 and TBM formulations. Per CMC reviewer Dr. Nina Ni, these changes are found to be acceptable.

Inserter

Two different inserters (THI-001 and SHI-001) were used in the pivotal Phase 3 study (Study M360-L102). The original two-handed inserter (THI-001) was used for the first 760 women. Enrollment was temporarily suspended due to reports from investigators of difficult placements, placement failures, and the need for cervical dilation. A single-handed inserter (SHI-001) was (b) (4) used in the subsequently enrolled 991 women. The Sponsor intends to market Liletta with a modified two-handed inserter (THI-002). Therefore, the Sponsor conducted Study M360-L104 to support the use of the new inserter. Considering Study M360-L104 did not sufficiently address Agency's concerns on potential infection or late complication after insertion due to small sample size (100 subjects) and short duration of assessment (24 hours), the medical team will request post-marketing evaluation to assess the inserter THI-022 on ease of Liletta placement, adverse events (AE) and expulsions, infections and other AEs that may be related to the insertion procedure.

Drug-Drug Interactions (DDI):

No clinical DDI study was conducted under this NDA. Contraceptive effect of Liletta is mediated via the direct release of LNG into the uterine cavity and thus is unlikely to be affected by drug interactions via enzyme induction or inhibition.

Specific Populations:

Renal / Hepatic impairment:

No dedicated study was conducted to evaluate the effect of renal or hepatic impairment on the disposition of Liletta. Of 1545 subjects for Liletta efficacy analysis in the Phase 3 study (Study M360-L102), 29 subjects had hepatic disorder. No significant or additional adverse events associated with Liletta use have been noted for these subjects. Due to mainly local action of Liletta, the efficacy is not expected to be affected by renal or hepatic impairment. Plasma concentration of LNG could be elevated in women with impaired renal or hepatic function. However, considering the systemic exposure LNG in Liletta is much lower than that in LNG-containing oral contraceptives, use of Liletta in women with renal or hepatic impairment is not expected to be of a safety concern.

Pediatric study:

The Sponsor has requested the exemption from Pediatric Research Equity Act (PREA), as Liletta does not contain a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration. The Agency agreed with PREA exemption (pre-NDA meeting minutes, DARRTS on October 17 2013).

Safety and efficacy of LILETTA were studied in 11 subjects aged 16 – 17 years in the Phase 3 study (Study M360-L102). There were no pregnancies in these females. Eight subjects experienced adverse events; of these, nasopharyngitis (3/11) and bacterial vaginitis (2/11) occurred in more than 1 subject. Efficacy is expected to be the same for postpubertal females under the age of 16 as for users 16 years and older.

Body Mass Index (BMI)

Out of 1751 subjects in pivotal Phase 3 study (Study M360-L102), 958 subjects (55%) were overweight (BMI from 25 to 30 kg/m²) or obese (BMI ≥ 30 kg/m²). There was no difference in contraceptive efficacy based on BMI. In addition, no clinically significant differences in safety profiles were observed when analyzed by BMI. The effect of BMI on LNG exposure from Liletta was assessed in 21 non-obese (BMI ≤ 30 kg/m²) and 20 obese women from day 7 to Month 30 and 166 non-obese and 77 obese women at Month 36 in the Phase 3 study. For the total duration of 36 months of use, plasma LNG concentrations were about 25% – 40% lower in obese subjects than those in non-obese subjects.

Race

Out of 1751 subjects in pivotal Phase 3 study (Study M360-L102), 1370 (78.4%) were Caucasians, and 232 (13.3%) were African American. There was no apparent effect of race on contraceptive efficacy. In addition, no clinically significant differences in safety profile have been noted with the Liletta when analyzed by race. Assessment of the effects of race on LNG exposure was performed on 40 subjects through Month 30 and 243 subjects at Month 36. No apparent impact of race on LNG concentrations was detected.

Bioanalytical Method Validation:

LNG plasma concentrations were determined using a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) method for Study M360-L102. Acceptance criteria and assay performance for LNG were found to be acceptable.

2 QUESTION BASED REVIEW

2.1 GENERAL ATTRIBUTES

2.1.1 What is Liletta? Are there any similar products in the US market?

Liletta is a LNG- IUS indicated for the prevention of pregnancy for up to 3 years. Liletta contains 52 mg of LNG. The initial *in vivo* release rate is 18.6 µg/day. This rate decreases progressively to approximately

16.3 µg/day at 1 year, 14.3 µg/day at 2 years, and 12.6 µg/day at 3 years after insertion. The average *in vivo* release rate of LNG is approximately 15.6 µg /day over a period of 3 years.

Other products that are currently marketed in the US are Mirena® and Skyla® and they were approved in 2000 (NDA 21225) and 2010 (NDA 203159), respectively. A comparison among the above three IUS products are presented in **Table 2**.

Table 2 Comparison of Liletta with currently approved IUS products Mirena® and Skyla®

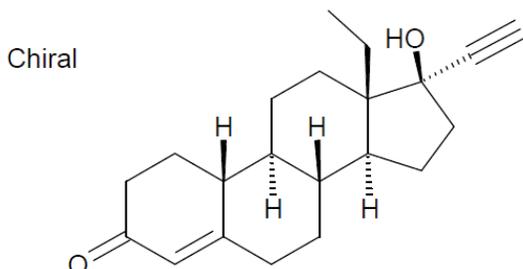
| IUS product | Duration of use | Total LNG (drug load) | Initial release rate | Release rate after 3- or 5-year of use |
|-------------|-----------------|-----------------------|----------------------|--|
| Liletta | 3 years | 52 mg | 18.6 µg/day (day 1) | 12.6 µg/day (3-year) |
| Mirena® | 5 years | 52 mg | 20 µg/day | 10 µg/day (5-year) |
| Skyla® | 3 years | 13.5 mg | 14 µg/day (day 24) | 5 µg/day (3-year) |

2.1.2 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

Active substance:

The active pharmacologic ingredient in Liletta is LNG. LNG USP is a (b) (4) powder chemically described as (-)-13-Ethyl-17-hydroxy-18, 19-dinor-17 alpha-pregn-4-en-20-yn-3-one. The structural formula is presented in **Figure 1**.

Figure 1 LNG chemical structure



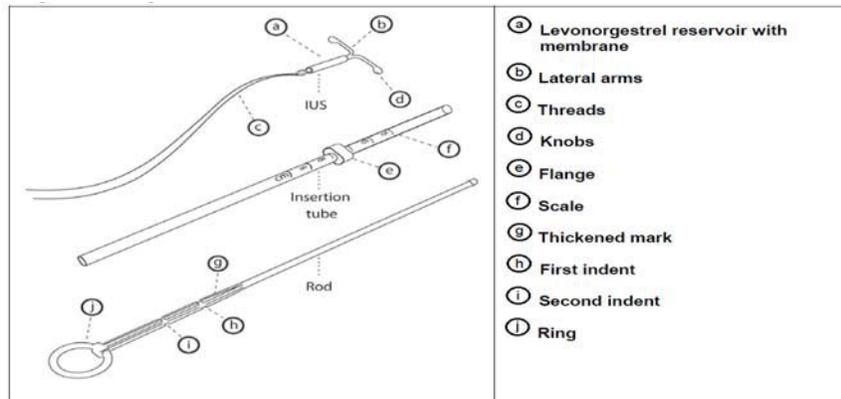
$C_{21}H_{28}O_2$

MW 312.45

Formulation:

As shown in **Figure 2**, Liletta consists of cylindrical drug reservoir mounted on a low density polyethylene T-frame. The drug reservoir is composed of a mixture of 52 mg LNG and polydimethylsiloxane (PDMS) membrane which covers the reservoir and (b) (4). A polypropylene monofilament thread is attached to an eyelet at the base of the T-frame for IUS removal. The non-drug components of the delivery system include the intrauterine drug delivery system as well as a device inserter tube and its associated plunger rod.

Figure 2 Schematic illustrations of Liletta and Inserter



2.1.3 What is the proposed mechanism of action?

The contraceptive effect of Liletta is mainly achieved via local progestogenic effect within the uterine cavity and cervix, including thickening of cervical mucus which prevents passage of sperm through the cervix and inhibition of sperm capacitation or survival, and alteration of the endometrium. Ovulation inhibition was not assessed in the pivotal Phase 3 study. Nonetheless, ovulation inhibition does not appear to play a significant role in IUS efficacy. In clinical trials with other LNG-releasing IUSs, ovulation was inhibited in some women but most cycles were ovulatory.

2.1.4 What are the clinical and clinical pharmacology data submitted to support the approval of Liletta?

In support of this NDA, the Sponsor conducted a pivotal Phase 3 study (Study M360-L102) and three supporting studies including two Phase 1 clinical studies (Study M360-L103, Study M360-L104) and a Phase 3 study (Study Levosert-20) to evaluate contraceptive efficacy and safety parameters of Liletta as well as the successful placement of Liletta using different inserters.

Study M360-L102:

A pivotal Phase 3, open-label safety and efficacy study of Liletta conducted in US for the indication of prevention of pregnancy for up to 3 years. The study is currently ongoing to evaluate the safety and efficacy of Liletta up to 5 years.

o Study Design:

This is a Phase 3 multi-center, open-label, evaluation of the efficacy of a LNG-releasing IUS. Two groups of women were enrolled and treated with Liletta: 1600 subjects 16-35 years old were enrolled to evaluate contraceptive efficacy (Efficacy Group) and 151 subjects 36-45 years old were enrolled to evaluate safety (Non-efficacy Group) in older women who more commonly choose intrauterine contraceptives. The demographic information of the study subjects are summarized in **Table 3**:

Reviewer's Notes:

The initial study design included Mirena® as a comparator for European regulatory filing of LNG20 IUS. The Mirena arm was stopped after 159 subjects had been enrolled. The limited Mirena data in this trial are not adequate to support any comparative conclusions regarding Liletta, but may be useful in comparing LNG exposure between Mirena® and Liletta.

Table 3 Demographic information in study subjects in Study M360-L102

| | Efficacy Group | Non-Efficacy Group |
|---------------------|--------------------------|---------------------------|
| Subjects number (N) | 1600 | 151 |
| Age* | 26.2 ± 4.4 (18-35) years | 39.6 ± 2.7 (36-45) years |
| Nulliparous | 62% | 15% |
| Race | 78.3 % white, | 79.5% white |

| | | |
|---|--------------------------------------|---------------------------------------|
| | 13.3% African American 3.8% Asian | 13.2% African American 4.6 % Asian |
| Average BMI | 26.8 kg/m ² | 28.6 kg/m ² |
| % of subjects with BMI 30- 39.9 kg/m ² | 24% | 36% |
| % of subjects with BMI ≥ 40 kg/m ² | 5% | 9% |

- Primary Efficacy Results:
There were 2 on-treatment pregnancies in the Efficacy Group, both occurring in the first year. The contraceptive efficacy was evaluated using Pearl Index (PI) defined as the number of pregnancies per 100 woman-years. The PI and 95% confidence interval for Years 1, 2, and 3 for the Modified Intent-to-Treat (MITT) group were summarized in **Table 4**.

Table 4 Primary efficacy analysis for Study M360-L102

| Liletta MITT Population (16-35 years old), N=1545 | | | |
|--|-------------|------|------------|
| Year | Pregnancies | PI | 95% CI |
| Year 1 | 2 | 0.20 | 0.02, 0.73 |
| Year 2 | 0 | 0.14 | 0.02, 0.52 |
| Year 3 | 0 | 0.12 | 0.01, 0.44 |
| Cumulative- 3 years | 2 | 0.12 | 0.01, 0.44 |

- Pharmacokinetic (PK) Assessment
LNG plasma concentrations at various times following Liletta placement were determined in a subset of 40 subjects at Day 7 and Months 1, 6, 12, 18, 24, and 30. In addition, LNG plasma concentrations were measured in 243 subjects who completed the Phase 3 study at Month 36.
- Assessment on LNG *in vivo* release rate:
Ex vivo analysis: LNG release rate was determined by residual drug content analysis of 74 samples that removed or expelled over the course of the Phase 3 study M360-L102.

Study M360-L103: A supportive Phase 1 study to assess the successful placement of Liletta using the SHI-001 inserter in nulliparous and parous women aged 18- 45 years.

Study M360-L104: A supportive Phase 1 study to assess the successful placement of Liletta using the new optimized THI-002 inserter in nulliparous and parous women aged 18- 45 years.

Study Levosert-20: A Phase 3, randomized study to assess to compare the efficacy and safety of the LNG-IUS product and Mirena® in patients with menorrhagia. The sponsor did not make any claim in regards to menorrhagia in the sponsor’s proposed label. The study was submitted mainly to support the safety of Liletta. In addition, LNG plasma concentrations were measured up to 3 years in patients with either Mirena® or LNG-IUS product.

Reviewer’s note:

Per Medical reviewer Dr. Dan Davis, the data from this study were not included in the overall summary of safety (refer to meeting minutes for Type C meeting held on 06/26/2012). In addition, the formulation, manufacture site and inserter of LNG-IUS for Study Levosert-20 are all different from those for the pivotal phase 3 study and the commercial product. The PK information from this study does not provide any significant relevance and therefore, it was not reviewed.

Clinical Pharmacology Studies:

No dedicated clinical pharmacology studies were conducted with Liletta. LNG plasma concentrations at various times following Liletta placement were determined in a subset of 40 subjects at Day 7 and

Months 1, 6, 12, 18, 24, and 30. In addition, LNG plasma concentrations were measured in 243 subjects who completed the Phase 3 study at Month 36.

2.2 GENERAL CLINICAL PHARMACOLOGY

2.2.1 What are the PK characteristics of Liletta?

No dedicated PK study was conducted for Liletta. In the Phase 3 study (Study M360-L102), LNG plasma concentrations were determined from Day 7 to Month 30 in a subset of 57 subjects (16 to 35 years of age). Among those, 40 subjects received Liletta, and 17 subjects received Mirena®. At Month 36, LNG plasma concentrations were determined in 243 subjects who received Liletta and 36 subjects who received Mirena®. LNG plasma concentrations at various times following Liletta placement are shown in **Table 5**.

Table 5 Plasma LNG Concentrations (mean ± SD, pg/mL) following Liletta placement in Study M360-L102

| Initial (Day-7) (N = 40) | Month-1 (N = 40) | Month-6 (N = 36) | Month-12 (N = 33) | Month-18 (N = 30) | Month-24 (N = 29) | Month-30 (N = 9) | Month-36 (N = 243) |
|-----------------------------|---------------------|---------------------|----------------------|----------------------|----------------------|---------------------|-----------------------|
| 252 ± 123 | 216 ± 75 | 195 ± 69 | 170 ± 50 | 149 ± 41 | 147 ± 46 | 135 ± 28 | 135 ± 51 |

2.2.2 Are LNG concentrations from Liletta comparable to that in Mirena®?

Yes. The PK data from study M360-L102 showed similar LNG concentrations released from Liletta and Mirena® (**Table 6**).

Table 6 LNG concentrations from Liletta and Mirena® in Study M360-L120

| | Day-7 | Month-1 | Month-6 | Month-12 | Month-18 | Month-24 | Month-30 | Month-36 |
|---------|-----------------------|----------------------|----------------------|----------------------|----------------------|----------------------|---------------------|-----------------------|
| Liletta | 310 ± 140 (N = 21) | 248 ± 83 (N = 21) | 230 ± 67 (N = 20) | 192 ± 36 (N = 18) | 169 ± 38 (N = 16) | 178 ± 38 (N = 15) | 137 ± 34 (N = 6) | 146 ± 48 (N = 166) |
| Mirena | 341 ± 145 (N = 17) | 261 ± 93 (N = 16) | 222 ± 56 (N = 15) | 187 ± 42 (N = 12) | 169 ± 32 (N = 9) | 150 ± 29 (N = 9) | 172 (N = 1) | 148 ± 72 (N = 23) |

* All subjects for PK assessment in Mirena treatment group are non-obese. Therefore, PK data only in non-obese subjects were presented for Liletta for a fair comparison.

2.2.3 What are the ADME characteristics of LNG released from LILETTA

The ADME of LNG after release from Liletta is described in Section 1.3.

2.2.4 Is there a depot effect after Liletta removal?

The Sponsor did not assess LNG plasma concentrations following Liletta Removal. In Phase 3 Study M360-L102, a subset of subjects were selected to evaluate for return of menses after Liletta removal. Out of 183 study subjects, 180 subjects (98.4%) had a returned menses within 3 months.

2.3 INTRINSIC FACTORS

2.3.1 What intrinsic factors (race, age (we also talked about young adolescents) body weight, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on contraceptive efficacy

Relationship between BMI and Exposure

The effect of BMI on LNG exposure was assessed in 40 subjects through Month 30 and 243 subjects at Month 36 in the Phase 3 study (Study M360-L102). As shown in **Figure 4**, women with higher BMI tends to have a lower LNG systemic exposure. In particular, plasma LNG concentrations were 25% –

40% lower in obese subjects than in non-obese subjects (**Table 7**). Additional data are needed to reach solid statistical conclusions on the effect of body weight on LNG plasma concentrations from Liletta.

Figure 4 Mean Plasma LNG Concentrations in Obese and Non-obese Subjects Following Liletta Placement in study M360-L102

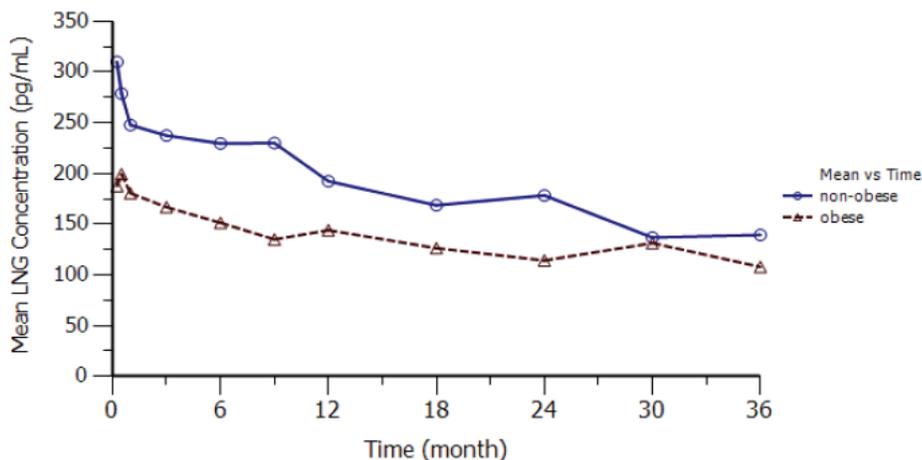


Table 7 Mean Plasma LNG Concentrations in Obese and Non-obese Subjects following Liletta placement in study M360-L102

| | Week 1 | Month 1 | Month 6 | Month 12 | Month 18 | Month 24 | Month 30 | Month 36 |
|------------------|-----------------------|----------------------|----------------------|----------------------|----------------------|----------------------|---------------------|-----------------------|
| Non-obese | 310 ± 140 (N = 21) | 248 ± 83 (N = 21) | 230 ± 67 (N = 20) | 192 ± 36 (N = 18) | 169 ± 38 (N = 16) | 178 ± 38 (N = 15) | 137 ± 34 (N = 6) | 146 ± 48 (N = 166) |
| Obese | 188 ± 53 (N = 19) | 180 ± 45 (N = 19) | 151 ± 40 (N = 16) | 144 ± 52 (N = 15) | 126 ± 33 (N = 14) | 114 ± 27 (N = 14) | 131 ± 15 (N = 3) | 111 ± 50 (N = 77) |

Despite a decreased LNG systemic exposure in obese women, there was no difference in contraceptive efficacy based on BMI; no pregnancies occurred in obese (BMI ≥ 30) subjects. No impact of lower plasma LNG on efficacy may be attributable to the local action of Liletta in the uterus. In addition, no clinically significant differences in safety profiles have been observed when analyzed by BMI.

Relationship between Renal/Hepatic Impairment and Exposure/Contraceptive efficacy and safety

No dedicated study was conducted to evaluate the effect of renal or hepatic impairment on the disposition of Liletta. Of 1545 subjects for Liletta efficacy analysis in the Phase 3 study, 29 subjects have hepatic disorder. No significant or additional adverse events have been noted for these subjects.

Due to mainly local action of Liletta, the efficacy is not expected to be affected by renal or hepatic impairment. Plasma concentration of LNG could be elevated in women with impaired renal or hepatic function. However, considering the systemic exposure of LNG in Liletta is much lower than that in LNG-containing oral contraceptives, use of Liletta in women with renal or hepatic impairment is not expected to be of safety concern.

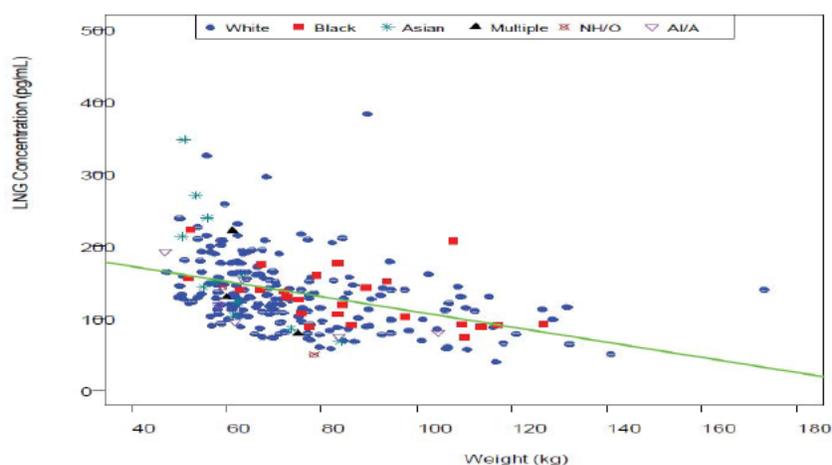
Relationship between Race and Exposure/Contraceptive efficacy and safety

Assessment of the effects of race on LNG exposure was performed on 40 subjects from Day 7 to Month 30 and 243 subjects at Month 36 (**Figure 5**). The effect of race on drug exposure was performed on White and Black/African American subgroups. The Asian and Multiple Races Indicated were not included in the evaluation due to the insufficiency of the sample size. No impact of race on LNG concentration was detected at any of the time points evaluated through Month 24 and in the main Phase 3 study (all subjects) at Month 36. There were insufficient data for the Month 30 time point to include in this analysis.

Additional data are needed for solid statistical conclusions on the impact of race on LNG plasma concentrations from Liletta.

There was no apparent effect of race on contraceptive efficacy. In addition, no clinically significant differences in safety profile have been noted with the Liletta when analyzed by race.

Figure 5 LNG Concentrations in subjects with different races at Month 36 following Liletta placement (NH/O: Native Hawaiian or Other Pacific Islander; AI/A: American Indian or Alaska Native)



2.4 EXTRINSIC FACTORS

No clinical DDI study was conducted under this NDA. Contraceptive effect of Liletta is mediated via the direct release of LNG into the uterine cavity and is unlikely to be affected by drug interactions via enzyme induction or inhibition.

2.5 GENERAL BIOPHARMACEUTICS

2.5.1 What is the release rate of LNG from Liletta?

LNG release rate was determined by residual drug content analysis of 74 samples that removed or expelled over the course of the Phase 3 study. In particular, the drug content and time of exposure of the samples analyzed were fit by an exponential regression to calculate the initial and average *in vivo* release rate over the duration of the study. Using this method, the initial *in vivo* release rate is estimated to be 18.6 µg/day. The release rate decreases to 16.3 µg/day at 1 year, 14.3 µg/day at 2 years, and 12.6 µg/day after 3 years. The average *in vivo* release rate of LNG is approximately 15.6 µg/day over a period of 3 years. Per ONDAQ reviewer Dr. Kelly Kitchens, the estimated *in vivo* release rates are acceptable.

2.5.2 Is the clinical formulation same to the TBM formulation?

Formulation composition (b) (4) between the Phase 3 and TBM products (Table 8). There are minor changes in the manufacturing process for the commercial product (b) (4). Based on *f2* test, *in vitro* drug release profiles are comparable between Phase 3 and TBM formulations. Per CMC reviewer Dr. Nina Ni, the proposed changes in manufacturing process are acceptable.

Table 8 Phase 3 and TBM Drug Product Quantitative Composition

| Component | Function | Quantity |
|------------------------|--|-----------------------|
| Drug Reservoir | Reservoir of LNG active substance | 1 unit (b) (4) |
| Levonorgestrel (b) (4) | Drug substance | 52.0 mg |
| Silicone base | (b) (4) | (b) (4) |

| | | |
|---|--|-----------------------|
| Tetra-n-propyl silicate | (b) (4) | |
| Stannous octoate | (b) (4) | |
| (b) (4) | (b) (4) | |
| T-frame | T-frame with radio opaque agent | 1 unit |
| Low Density Polyethylene (LDPE) | (b) (4) | (b) (4) |
| Barium sulfate | Radio opaque agent | (b) (4) |
| Polydimethylsiloxane (PDMS) membrane | (b) (4) | 1 unit (b) (4) |
| (b) (4) | | N/A* |
| Polypropylene thread copper | Removal thread | 1 unit |

Inserters

Two different inserters (THI-001 and SHI-001) were used in the pivotal Phase 3 study (Study M360-L102). The original two-handed inserter (THI-001) was used for the first 760 women. Enrollment was temporarily suspended due to reports from investigators of difficult placements, placement failures, and the need for cervical dilation. A single-handed inserter (SHI-001) was (b) (4) used for the 991 women that were subsequently enrolled. As shown in **Table 9**, contraceptive efficacy as evaluated by pearl index (PI) does not appear to be affected by the inserter used to place the IUS within the uterus.

Sponsor intends to market Liletta with a modified two-handed inserter (THI-002) that is a redesign of the THI-001 inserter. (b) (4)

(b) (4) The Sponsor intends to market Liletta with a modified two-handed inserter (THI-002). Therefore, the Sponsor conducted Study M360-L104 to support the use of the new inserter. Considering Study M360-L104 did not sufficiently address Agency's concerns on potential infection or late complication after insertion due to small sample size (100 subjects) and short duration of assessment (24 hours), the medical team will request post-marketing evaluation to assess the inserter THI-022 on ease of Liletta placement, adverse events (AE) and expulsions, infections and other AEs that may be related to the insertion procedure.

Table 9 Pearl Index for Liletta Subjects in the Efficacy Group by Inserter Type (Study M360-L102)

| | THI-001 Inserter (N= 611) | SHI-001 Inserter (N = 934) |
|--------|----------------------------------|-----------------------------------|
| Year 1 | 0.19 (0.00, 1. 06) | 0.22 (0.01, 1.21) |
| Year 2 | 0.11 (0.00-0.60) | 0.22 (0.01, 1.21) |
| Year 3 | 0.08 (0.00-0.46) | 0.22 (0.01, 1.21) |

2.6 ANALYTICAL SECTION

2.6.1 What bioanalytical methods are used to assess concentrations?

LNG plasma concentrations were determined with a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) method. The detailed analytical conditions are presented in **Table 10**.

Table 10 LC-MS/MS for plasma LNG concentrations

| Parameter | QC Samples | Standard Curve Samples |
|--|-------------------|--------------------------------------|
| Concentration (pg/mL) | 75, 400, 800 | 25.0, 50.0, 100, 250, 500, 900, 1000 |
| Interday Precision (% CV) | 6.1 to 8.2 | 2.8 to 8.0 |
| Interday Accuracy (% RE) | 0 to -1.4 | -1.5 to 1.6 |
| Linearity (Range of R ² values) | N/A | 0.9937 to 0.9990 |

| | | |
|---|-----|--------------|
| Linear Range (ng/mL) | N/A | 25.0 to 1000 |
| Sensitivity/Lower Limit of Quantitation (pg/mL) | N/A | 25.0 |

Acceptable criteria and assay performance for LNG were in compliance with the *bioanalytical Method Validation Guidance* and the bioanalytical methods were found to be acceptable.

3 DETAILED LABELING RECOMMENDATIONS

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use LILETTA™ safely and effectively. See full prescribing information for LILETTA.

LILETTA (levonorgestrel-releasing intrauterine system).
Initial U.S. Approval: 20xx

INDICATIONS AND USAGE

LILETTA is a sterile, levonorgestrel, (b) (4) releasing intrauterine system (b) (4) (b) (4) indicated for prevention of pregnancy for up to 3 years (b) (4) (1)

DOSAGE AND ADMINISTRATION

- Release rate of levonorgestrel (LNG) is 18.6 mcg/day initially and declines progressively to approximately 16.3 mcg/day at 1 year, 14.3 mcg/day at 2 years, and 12.6 mcg/day at 3 years after insertion (b) (4) (b) (4) LILETTA can be removed at any time but must be removed by the end of the third year. (2)
- To be inserted by a trained healthcare provider using strict aseptic technique. Follow insertion instructions exactly as described. (2.1)
- Patient should be re-examined and evaluated 4 to 6 weeks after insertion and once a year thereafter, or more frequently if clinically indicated. (2.3)

DOSAGE FORMS AND STRENGTHS

- One intrauterine system consisting of a T-shaped polyethylene frame with a drug reservoir containing 52 mg levonorgestrel, packaged within a sterile inserter. (3)

CONTRAINDICATIONS

- Pregnancy or (b) (4) pregnancy; (b) (4) (b) (4)
- Congenital or acquired uterine anomaly (b) (4) that distorts the uterine cavity (4)
- Acute pelvic inflammatory disease or a history of pelvic inflammatory disease unless there has been a subsequent intrauterine pregnancy. (4)
- Postpartum endometritis or infected abortion in the past 3 months (4)
- Known or suspected uterine or cervical neoplasia (4)
- Known or suspected breast cancer or other progestin-sensitive cancer; (b) (4) (4)
- Uterine bleeding of unknown etiology (4)

- Untreated acute cervicitis or vaginitis, (b) (4) (b) (4) or other lower genital tract infections (b) (4) (4)
- Acute liver disease or liver tumor (benign or malignant) (4)
- (b) (4) increased susceptibility to pelvic infections (4)
- A previously inserted IUS that has not been removed (4)
- Hypersensitivity to any component of (b) (4) LILETTA (4)

WARNINGS AND PRECAUTIONS

- Remove LILETTA if pregnancy occurs with LILETTA in place and LILETTA is in the uterus. (b) (4) If pregnancy occurs, there is increased risk of ectopic pregnancy including loss of fertility, pregnancy loss, septic abortion (including septicemia, shock and death) and premature labor and delivery. (5.1, 5.2)
- Group A streptococcal infection has been reported; strict aseptic technique is essential during insertion. (5.3)
- Before using LILETTA, consider the risks of PID. (5.4)
- Bleeding patterns become altered, may remain irregular and amenorrhea may ensue. (5.5)
- Perforation may occur and reduce contraceptive effectiveness. Risk is increased if inserted in women with fixed retroverted uteri, during lactation, and postpartum. (5.6)
- Partial or complete expulsion may occur. (5.7)
- Evaluate persistent enlarged ovarian follicles. (5.8)

ADVERSE REACTIONS

The most common adverse reactions reported in clinical trials (> 10% users) are (b) (4) vaginal infections, and acne. (6)

To report SUSPECTED ADVERSE REACTIONS, contact xxx at 1-xxx-xxx-xxxx or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised 1001/20145

7 DRUG INTERACTIONS

No drug-drug interaction studies have been conducted with LILETTA.

Contraceptive effect of LILETTA is mediated via the direct release of LNG into the uterine cavity and is unlikely to be affected by drug interactions via enzyme induction or inhibition.

(b) (4)



8 USE IN SPECIFIC POPULATIONS

8.4 Pediatric Use

Safety and efficacy of LILETTA have been established in (b) (4) female of reproductive age. (b) (4)
(b) (4)
(b) (4) Efficacy is expected to be the same for postpubertal females under the age of 16 as for users 16 years and older. Use of this product before menarche is not indicated [See Specific Populations (12.3)].

8.5 Geriatric Use

LILETTA has not been studied in women over age 65 and is not (b) (4)
indicated for postmenopausal women.

8.6 Hepatic Impairment

No studies were conducted to evaluate the effect of hepatic disease on the disposition of levonorgestrel released from LILETTA [see Contraindications (4)].

8.7 Renal Impairment

No studies were conducted to evaluate the effect of renal disease on the disposition of levonorgestrel released from LILETTA [see Contraindications (4)].

8.8 Obesity

The safety and efficacy of Liletta have been evaluated in overweight, obese, and morbidly obese patients. There was no apparent effect of BMI or body weight on contraceptive efficacy [See Specific Populations (12.3)].

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The local mechanism by which continuously released LNG provides contraception has not been conclusively demonstrated. Studies of (b) (4) LNG-releasing IUSs suggest several mechanisms for pregnancy prevention: (b) (4) prevention of fertilization due to the thickening of the cervical mucus (b) (4) which inhibits sperm passage through the cervix, and inhibition of sperm mobility and function (capacitation) (b) (4) and alteration of the endometrium.

12.2 Pharmacodynamics

LILETTA has mainly local progestogenic effects in the uterine cavity. (b) (4)
(b) (4) high local (b) (4) concentration of (b) (4) LNG (b) (4) lead to morphological changes including stromal pseudodecidualization, glandular atrophy, a leukocytic infiltration, and a decrease in glandular and stromal mitoses. (b) (4) Changes in the uterine endometrium may lead to alterations in the menstrual bleeding pattern [see *Warnings and Precautions (5.5)*].

In clinical trials with other (b) (4) LNG-releasing IUSs, ovulation was inhibited in some women but most cycles were ovulatory. (b) (4)

(b) (4)

12.3 Pharmacokinetics

Absorption

Low doses of (b) (4) LNG are administered into the uterine cavity with the LILETTA intrauterine delivery system. The initial in vivo release rate is 18.6 µg/day and decreases to 16.3 µg/day at 1 year, 14.3 µg/day at 2 years, and 12.6 µg/day after 3 years.

(b) (4)

In the phase 3 study, systemic LNG concentrations were assessed in a subset of subjects through Month 30 and in all subjects at Month 36. Steady-state plasma LNG concentrations following placement of Liletta are shown in Table 1.

Table 1 Plasma LNG Concentrations (mean ± SD, pg/mL) Following Liletta Placement

| <u>Initial (7 days)</u> | <u>6 Months</u> | <u>12 Months</u> | <u>24 Months</u> | <u>30 Months</u> | <u>36 Months</u> |
|-------------------------|-----------------|------------------|------------------|------------------|------------------|
| <u>(N = 40)</u> | <u>(N = 36)</u> | <u>(N = 33)</u> | <u>(N = 29)</u> | <u>(N = 9)</u> | <u>(N=243)</u> |
| <u>252 ± 123</u> | <u>195 ± 69</u> | <u>170 ± 50</u> | <u>147 ± 46</u> | <u>133 ± 28</u> | <u>135 ± 51</u> |

Distribution

The apparent volume of distribution of (b) (4) at steady-state following oral administration is reported to be approximately 1 (b) (4) L/kg. It is about 98.9% protein-bound, principally to sex hormone binding globulin (SHBG) and, to a lesser extent, serum albumin (b) (4).

Metabolism

Following absorption, levonorgestrel is conjugated at the 17 β -OH position to form sulfate conjugates and, to a lesser extent, glucuronide conjugates in serum. Significant amounts of conjugated and unconjugated 3 α , 5 β -tetrahydrolevonorgestrel are also present in serum, along with much smaller amounts of 3 α , 5 α -tetrahydrolevonorgestrel and 16 β -hydroxylevonorgestrel (b) (4). Levonorgestrel and its phase I metabolites are excreted primarily as glucuronide conjugates (b) (4). Metabolic clearance rates may differ among individuals by several-fold, and this may account in part for wide individual variations in levonorgestrel concentrations seen in individuals using levonorgestrel-containing contraceptive products. In vitro studies have demonstrated that oxidative metabolism of levonorgestrel is catalyzed by CYP enzymes, especially CYP3A4.

Excretion

About 45% of levonorgestrel and its metabolites are excreted in the urine and about 32% are excreted in feces, mostly as glucuronide conjugates (b) (4). The elimination half-life of levonorgestrel after a single oral administration is approximately 13.9 \pm 3.2 hours (b) (4).

Specific Populations

Pediatric: Safety and efficacy of LILETTA have been established in (b) (4) female of reproductive age. (b) (4) The LILETTA clinical trial included 11 subjects aged 16 to 17 years; no pregnancies occurred in these subjects.

(b) (4)

Race: (b) (4) (b) (4) The LILETTA clinical trial included 199 (13%) Black/African American subjects and 226 (15%) subjects of Hispanic ethnicity. Race does not appear to affect LNG concentrations following Liletta insertion.

(b) (4)

Obesity: Liletta clinical trial included overweight (24%), obese (24%), and morbidly obese (5%) women. LNG systemic exposure decreased with increasing body weight; however, there was no apparent effect of body mass index (BMI) or body weight on contraceptive efficacy.

CLINICAL PHARMACOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA Number: 206229

Applicant: Medicines360

Stamp Date: 4/30/2014

Drug Name: (b) (4)

NDA Type: Original

On **initial** overview of the NDA/BLA application for filing:

| | Content Parameter | Yes | No | N/A | Comment |
|---|--|-----|----|-----|---|
| Criteria for Refusal to File (RTF) | | | | | |
| 1 | Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials? | | X | | There were changes in manufacturing process of the product which will be reviewed by ONDQA. |
| 2 | Has the applicant provided metabolism and drug-drug interaction (DDI) information? | X | | | The metabolism and drug-drug interaction information relying on other approved products were submitted. |
| Criteria for Assessing Quality of an NDA | | | | | |
| Data | | | | | |
| 3 | Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)? | X | | | |
| 4 | If applicable, are the pharmacogenomic data sets submitted in the appropriate format? | | | X | |
| Studies and Analyses | | | | | |
| 5 | Has the applicant made an appropriate attempt to determine the reasonable dose individualization strategy for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)? | | | X | The product has one strength only. |
| 6 | Did the applicant follow the scientific advice provided regarding matters related to dose selection? | X | | | |
| 7 | Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted in a format as described in the Exposure-Response guidance? | | X | | |
| 8 | Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics? | | | X | The product has one strength only. |
| 9 | Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective? | | | X | The applicant requests PREA exemption. |
| 10 | Did the applicant submit all the pediatric exclusivity data, as described in the WR? | | | X | The applicant requests PREA exemption. |

CLINICAL PHARMACOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

| | | | | | |
|----------------|--|---|--|---|--------------------------------------|
| 11 | Is the appropriate pharmacokinetic information submitted? | X | | | |
| 12 | Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label? | X | | | |
| General | | | | | |
| 13 | On its face, is the clinical pharmacology and biopharmaceutical section of the NDA organized in a manner to allow substantive review to begin? | X | | | |
| 14 | Is the clinical pharmacology and biopharmaceutical section of the NDA indexed and paginated in a manner to allow substantive review to begin? | X | | | |
| 15 | On its face, is the clinical pharmacology and biopharmaceutical section of the NDA legible so that a substantive review can begin? | X | | | |
| 16 | Are the clinical pharmacology and biopharmaceutical studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product? | X | | | |
| 17 | Was the translation from another language important or needed for publication? | | | X | No foreign documents were submitted. |

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? ___ Yes ___

Background

The sponsor submitted NDA 206229 for (b) (4), an intrauterine contraceptive, for the prevention of pregnancy for up to 3 years under 505(b)(2). (b) (4) contains 52 mg of levonorgestrel (LNG) for which sponsor claims that the initial release rate and release rate after 3 years are 18.6 ug/day and 12.6 ug/day, respectively. The pivotal phase 3 study M360-L102 is currently ongoing to evaluate the safety and efficacy of (b) (4) up to 5 years.

Clinical Studies

Sponsor conducted 3 clinical studies as described below.

1. M360-L102: A pivotal phase 3, open-label safety and efficacy study of (b) (4) conducted in US for the indication of prevention of pregnancy for up to 3 years in females of any body weight whether or not they have had a child. The study included 1751 women ages 16-45 years who received (b) (4) for up to 3 years. This study includes the following sub-reports:

- a. PK Report: Assessment of the systemic LNG concentration in a subset (57 subjects: 38 non-obese subjects + 19 obese subjects) of the efficacy group through Month 30 and in all subjects at Month 36
- b. Ex Vivo Report: An estimation of the in vivo release rate of LNG from (b) (4) over the planned duration of use

In study M360-L102, 2 different inserters were used to place (b) (4). The original two-handed inserter (THI-001) was used for the first 760 women. Enrollment was temporarily suspended due to reports from investigators of difficult placements, placement failures, and the need for cervical dilation. Medicines360 (b) (4) a single-handed inserter (SHI-001) that was used for the 991 women who were enrolled subsequently.

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2. M360-L103: A supportive phase 1 study [REDACTED] (b)(4) of the single handed inserter, SHI-001, conducted in US.

Study M360-L103 was conducted as it was requested by the Division during the meeting with the sponsor on September 17, 2013 (DARRTS October 17, 2013).

3. Levosert-20: A phase 3, randomized study to assess to compare the efficacy and safety of Levosert and Mirena (NDA 021225, intrauterine system indicated for prevention of pregnancy) in patients with menorrhagia.

The sponsor did not make any claim in regards to menorrhagia in the sponsor's proposed label. Study Levosert-20 was conducted with THI-001. Plasma concentration of LNG was measured up to 3 years in patients with either Mirena or Levosert to compare the LNG exposures from two products.

Request for Waiver of Pediatric Studies

The sponsor requested the exemption from Pediatric Research Equity Act (PREA) requirement.

Formulation

There were changes in the drug manufacturing process. The sponsor provided the information regarding the manufacturing changes (e.g., order of addition of materials, cooling steps, addition of curing solution) of phase 3 formulation and to-be-marketed formulation.

Phase 3 study, M360-L102 was conducted with 2 inserters (THI-001 and SHI-001). While Medicines and Healthcare products Regulatory Agency (MHRA), an European regulatory agency, reviewed the Levosert, MHRA was concerned about the [REDACTED] (b)(4) inserter tip. Based on MHRA's concern, THI-001 was modified to THI-002 [REDACTED] (b)(4)

[REDACTED]

Levosert is available in Europe with THI-002. Sponsor intends to market [REDACTED] (b)(4) with THI-002 in US. Sponsor considered this inserter change (THI-001 to THI-002) was a minor change. However, Division informed the sponsor that the extent to which THI-001 is supported by the data obtained from study M360-L102 will be determined during the NDA review. Sponsor was also advised that it is possible that findings identified during the NDA review process may trigger a request for further clinical data to support marketing of the THI-002 inserter even if such a need is not identified prior to the NDA submission (Meeting Minutes, DARRTS, October 17, 2013).

Figure 1 THI-001

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(b) (4)

| Inserter Component | Phase 3 Clinical Study (THI-001) | To be Marketed (THI-002) |
|-------------------------|----------------------------------|---|
| Tube | | |
| Inserter tube tip shape | (b) (4) |  |

Figure 3 Difference between THI-001 and THI-002 regarding the Tube

Comments to be conveyed to the sponsor in a 74-day letter:

Information request

- Submit drug exposure-response (e.g., secondary efficacy endpoints such as return to menses, return to fertility, and endometrial thickness) analyses for study M360-L102 referring to the Guidance for Industry - Exposure-Response guidance (April 2003).
- Submit the analysis assessing the effect of race on drug exposure and response (e.g., secondary efficacy endpoints such as return to menses, return to fertility, and endometrial thickness) for study M360-L102.
- Submit the analysis assessing the effect of race, body weight, and age on drug exposure of Levosert from the study Levosert-20.

Hyunjin Kim

Reviewing Pharmacologist

Date

Myong-Jin Kim

Team Leader/Supervisor

Date

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/s/

HYUNJIN KIM
06/27/2014

MYONG JIN KIM
06/27/2014

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/s/

LI LI
01/30/2015

MYONG JIN KIM
01/30/2015