CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208224Orig1s000

MEDICAL REVIEW(S)

Clinical Investigator Financial Disclosure
Review Template

Application Number: NDA 208224

Submission Date(s): November 18, 2015

Applicant: Bayer HealthCare Pharmaceuticals Inc.

Product: Levonorgestrel-releasing Intrauterine System

Reviewer: Ronald J. Orleans, MD

Date of Review: September 16, 2016

Covered Clinical Study (Name and/or Number): CSR PH-37274, Protocol 91665/310442

Was a list of clinical investigators provided:	Yes X	No ☐ (Request list from applicant)
Total number of investigators identified: 138 study sites each with many subinvestigators		
Number of investigators who are sponsor employees (including both full-time and part-time employees): None		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 2		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: • Investigator1 ("Principal and coordinating investigator"): $191,800.00 • Investigator 2 ("Principal and coordinating investigator"): $374,504.60 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes X	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes X	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 2		
Is an attachment provided with the reason:	Yes X	No ☐ (Request explanation from applicant)

Discuss whether the applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators*.[1] Also discuss whether these interests/arrangements, investigators who are sponsor employees, or lack of disclosure despite due diligence raise questions about the integrity of the data:

- If not, why not (e.g., study design (randomized, blinded, objective endpoints), clinical investigator provided minimal contribution to study data)
- If yes, what steps were taken to address the financial interests/arrangements (e.g., statistical analysis excluding data from clinical investigators with such interests/arrangements)

Briefly summarize whether the disclosed financial interests/arrangements, the inclusion of investigators who are sponsor employees, or lack of disclosure despite due diligence affect the approvability of the application.

The Applicant has adequately disclosed the financial arrangements made with the two clinical investigators who received significant payments from the Applicant. The potential for these payments to bias the study findings is minimal for the following reasons:

- Patients collected their own data about bleeding episodes and side effects
- Pregnancy tests were administered by other study personnel
- Both investigators were not solely responsible for consenting or enrolling subjects
- Results are reviewed by the study monitor from the subjects' source documents
- The two study sites enrolled a total of (b) (6) subjects or (b) (6) % of the total study population of 2,885 subjects.

[1] See [web address].

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

/s/

RONALD J ORLEANS
09/15/2016

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	208224
Priority or Standard	Standard
Submit Date(s)	November 18, 2015
Received Date(s)	November 18, 2015
PDUFA Goal Date	September 16, 2016
Division / Office	Bone, Reproductive and Urologic Products (DBRUP)/Office of Drug Evaluation III (ODE III)
Reviewer Name(s)	Ronald J. Orleans, M.D.
Review Completion Date	September 14, 2016
Established Name	Levonorgestrel-releasing intrauterine system
(Proposed) Trade Name	Kyleena
Therapeutic Class	Progestin-containing intrauterine device
Applicant	Bayer HealthCare Pharmaceuticals Inc.
Formulation(s)	Intrauterine system
Dosing Regimen	Insertion into the uterine cavity (5 year contraceptive efficacy)
Indication(s)	Contraception
Intended Population(s)	Women of childbearing age

Table of Contents

Table of Tables

Table of Figures

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Based on the data submitted in Bayer HealthCare Pharmaceutical's (the Applicant's) NDA submission, I recommend that NDA 208224 be approved for the indication of prevention of pregnancy for up to 5 years. This recommendation is based on the Applicant having demonstrated an acceptable Pearl Index (PI) and an acceptable safety profile for this product.

1.2 Risk Benefit Assessment

The PI for Kyleena (hereafter referred to as LCS16) was derived from the data obtained from the phase 3 clinical trial PH-37274, which is referred to in this review as the LCS16 efficacy study. The study was conducted in Europe, North America and South America and included women 18 to 35 years of age in whom an LCS16 insertion was at least attempted. Cycles in which back-up contraception was used were excluded from the PI analysis unless a pregnancy occurred in that cycle. The PI for Year 1 was calculated based on 2 pregnancies occurring over 16,207 28-day cycle equivalents.

Based on these data, the PI of LCS16 for Year 1 is **0.16 (0.02, 0.58)**. The cumulative 5-Year PI was calculated based on 13 pregnancies occurring over 57,313 28-day cycle equivalents and was calculated to be 0.29 (0.16, 0.50). The cumulative pregnancy rate estimated by the Kaplan-Meier method per 100 women at the end of the first year is 0.18 (0.04, 0.71) and the cumulative pregnancy rate at the end of five years is **1.44 (0.82, 2.53).** The PIs and Kaplan-Meier calculations provide sufficient evidence to support the efficacy of LCS16 for women who desire intrauterine contraception for up to 5 years.

The bulk of the LCS16 safety database is derived from a pooled analysis of data from the LCS16 efficacy study and the comparative phase 2 study (A46796) that was conducted in Europe. Study A46796 is referred to in this review as the "phase 2 study." The safety assessment for LCS16 was based on the Full Analysis Set (FAS), which was defined as all women who were enrolled and had an LCS16 insertion attempt. From the pooled studies, a total of 1,697 women were treated with LCS16. A total of 337 subjects (19.8%) completed the 3-year studies. (Only the phase 3 study included a 2-year extension for the LCS16 arm.) A total of 707 subjects in the LCS16 efficacy study entered the 2-year extension phase and 550 subjects completed the extension phase. The population was generally healthy 18 to 41-year old females, predominantly Caucasian, and requesting intrauterine contraception.

The adverse events profile of LCS16 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. A

review of laboratory tests, vital signs, bone mineral density, endometrial histology and other safety parameters that were measured also did not reveal any specific concerns.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None

1.4 Recommendations for Postmarket Requirements and Commitments

Based on the clinical trials data submitted to this NDA, standard post-marketing surveillance is recommended to further monitor the safety and efficacy of LCS16.

2 Introduction and Regulatory Background

Bayer HealthCare Pharmaceuticals Inc. (the Applicant) is seeking approval for a low-dose, levonorgestrel (LNG)-releasing intrauterine delivery system (LCS16) with the proposed indication of prevention of pregnancy for up to 5 years.

The development of LCS16 was started in parallel with the development of a smaller, lower-dose IUS, which was approved for marketing as Skyla on January 9, 2013. LCS16 contains a higher dose of LNG in its drug reservoir than Skyla (19.5 mg versus 13.5 mg) and has a proposed longer duration of contraceptive efficacy (5 years versus 3 years).

Two clinical studies were submitted to support the safety and efficacy of LCS16 for the proposed indication. A phase 2 dose-finding study (Study A46796) was completed with two different doses, LCS16 and LCS12, corresponding to initial *in vitro* release rates of 16 and 12 µg/day, respectively. The phase 3 clinical trial (Study PH-37274) was conducted with LCS12 and LCS16 for up 3 years with an extension up to 5 years for the LCS16 arm only.

2.1 Product Information

LCS16 IUS is composed of (1) the T-body, (2) a drug core of 19.5 mg LNG, and (3) a covering outer membrane. LCS16 is classified as a single entity drug-device combination product.

Reviewer Comment

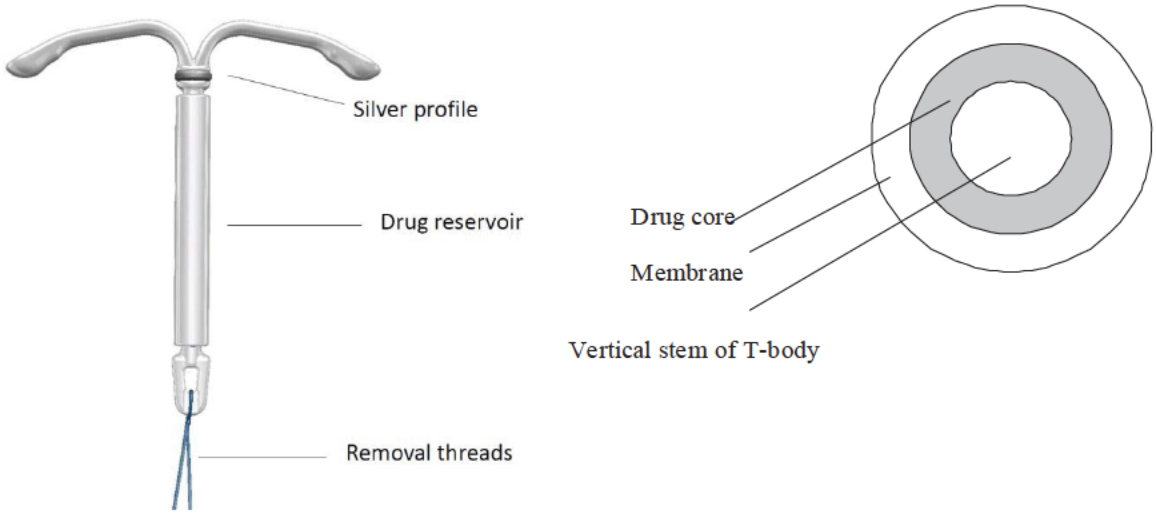
- *LCS16 is regulated as a drug product because it contains LNG. However, the applicator portion of the IUS is treated as a device, necessitating consultative reviews by CDRH. The applicator components include the insertion tube, the plunger, the flange, the handle, the slider and the thread lock.*

The IUS consists of a hormone-elastomer reservoir mounted on the vertical stem of a T-shaped polyethylene frame (T-body). The drug reservoir is composed of a mixture of 19.5 mg LNG and polydimethylsiloxane (PDMS). This reservoir is covered by a PDMS membrane (b) (4). The T-body has a loop at one end of the

vertical stem and two horizontal arms at the other end. The vertical stem contains a silver ring located close to the horizontal arms. Blue removal threads are attached to the loop of the T-body.

For the T-body of the LCS16 to-be-marketed product, the Applicant made post-trial modifications to the IUS formulation used in the phase 3 clinical trial. (b) (4)

Figure 1 LCS16



T-Body Cross-section of the drug reservoir

Compared with Mirena, which is approved for contraception for up to 5 years, LCS16 has a reduced LNG content and a smaller frame size and insertion tube diameter. Compared with Skyla, which is approved for contraception for up to 3 years, LCS16 provides a longer duration of use with the same size frame size and insertion tube diameter. Both LCS16 and Skyla include a silver ring to facilitate ultrasound detection and aid in differentiation of LCS16 and Skyla from other intrauterine systems during ultrasound examination. Skyla utilizes brown polyethylene removal threads. LCS16 will utilize blue polypropylene removal threads.

In both the phase 2 study and the LCS16 efficacy study, the same composition of the drug reservoir of LCS16 and LCS12 was used. To obtain the two dose strengths, different lengths of the same reservoir formulation were used.

LCS16 is placed in the uterus with a pre-loaded, ready-to-use inserter referred to in this review as the " (b) (4) inserter. With the (b) (4) inserter, the removal threads are

prefixed inside the shaft [redacted (b) (4)] However, the safety and efficacy of this inserter has been studied in 3 clinical trials as discussed in Section 7.3.5 of this review. In addition, this inserter has been approved for use with Bayer's other LNG IUSs, Skyla and Mirena. The inserter has an outer diameter of 3.8 mm (identical to the Skyla inserter, but smaller than the Mirena inserter, which has an outer diameter of 4.4 mm). The Applicant states that with the [redacted (b) (4)] inserter, the actual insertion procedure will remain unchanged.

2.2 Tables of Currently Available Treatments for Proposed Indications

Currently, there are 4 FDA-approved IUSs available for intrauterine contraception. These are Mirena, Skyla, Liletta and the copper-containing ParaGard® T 380A.

Mirena was first approved for marketing in Finland in 1990 and has been approved in the US since 2000. It is currently approved for (1) intrauterine contraception for up to 5 years and (2) the treatment of heavy menstrual bleeding for women who choose intrauterine contraception as their method of contraception. Mirena is currently approved in more than 100 countries. The reported 12-month pregnancy rate for Mirena was less than or equal to 0.2 per 100 women (0.2%) and the cumulative 5-year pregnancy rate was approximately 0.7 per 100 women (0.7%).

- Skyla was approved on January 9, 2013. It is a LNG-releasing intrauterine system indicated for the prevention of pregnancy for up to 3 years. Skyla's drug reservoir contains 13.5 mg of LNG. Skyla is currently approved in 50 countries. The one-year Pearl Index of Skyla is 0.41 (0.13, 0.96). The cumulative 3-Year Kaplan-Meier pregnancy rate was calculated to be 0.9% (0.5, 1.7).
- Liletta was approved on February 26, 2015. It is a LNG-releasing intrauterine system indicated for the prevention of pregnancy for up to 3 years. Liletta's drug reservoir contains 52 mg of LNG. The one-year Pearl Index of Liletta is 0.15 (0.02, 0.55). The cumulative 3-year Life Table pregnancy rate is 0.6% (0.5, 1.23).
- The ParaGard T 380A (NDA 018680) was originally approved in 1984. It is currently approved for intrauterine contraception for up to 10 years. The pregnancy rate in clinical studies of the ParaGard IUS has been less than 1 pregnancy per 100 women for each year of use.

Reviewer Comment

- *Bayer currently markets both Mirena and Skyla.*

2.3 Availability of Proposed Active Ingredient in the United States

LNG, the active drug component of LCS16, has a long history of use in combination with estrogen for gynecologic indications in the US. These indications include

contraception (oral and intrauterine use), the treatment of heavy menstrual bleeding and the treatment of vasomotor symptoms due to menopause.

2.4 Important Safety Issues with Consideration to Related Drugs

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

- Sexually transmitted infection and pelvic inflammatory disease with the subsequent risk of infertility
- Uterine perforation or expulsion
- Ectopic pregnancy
- Pregnancy loss or septic abortion if a pregnancy occurs with an IUD *in situ*.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

LCS16 was studied under Bayer's IND 73,505.

Prior to the initial submission of this IND, the Applicant requested a Type B Pre-IND Meeting to discuss the development program. This meeting was scheduled to take place on April 4, 2006; however, after reading the Division's draft comments, the Applicant determined that there were no further issues to be resolved and requested that the meeting be cancelled. The Division's final meeting minutes signed on May 1, 2006 included the following:

- The Division requested data for a minimum of 10,000 cycles for the first year of use.
- A total of 45% of these cycles should be from subjects in North America.
- The Division would consider the phase 3 study as a stand-alone pivotal study.

IND 73,505 was submitted by Bayer on August 27, 2007. The IND was opened with the phase 3 study A52238 (protocol 310442), entitled: "Multi-center, open-label, randomized study to assess the safety and contraceptive efficacy of two doses (*in vitro* 12 µg/24 h and 16 µg/24 h) of the ultra-low dose levonorgestrel contraceptive intrauterine systems (LCS) for a maximum of 3 years in women 18 to 35 years of age."

At the time of the IND submission, a 3-year phase 2 clinical study, A46796 (protocol 308901) was ongoing in Europe with the objective of determining an appropriate LNG dose for the IUSs. Based on the one-year interim analysis results from this study, both the LCS12 and LCS16 treatment arms were continued in the phase 2 study, and the phase 3 study was also designed with treatment arms for both doses. The interim results that supported these decisions were submitted to the Division on April 20, 2007 along with a summary of the planned phase 3 protocol and Bayer's responses to the Division's pre-IND clinical comments.

Several meetings and teleconferences were subsequently held under this IND:
On June 22, 2009, the Division provided three recommendations regarding Study A52238:

- Stratification of safety and efficacy results by parity
- Routine pregnancy testing at the 12- and 24-month visits
- Collection of data regarding the use of back-up contraception.

The request for routine pregnancy testing at the 12 and 24 month visits could not be accommodated as the study was already underway.

A Type B End-of-Phase 2 Meeting was held on November 24, 2009 to discuss Clinical and Clinical Pharmacology topics.

At this meeting, Bayer's proposal to extend the LCS16 arm of the study was discussed with the Division. The Division's comments were incorporated in Protocol Amendment 5, which was submitted on February 3, 2010 and provided for the extension of the LCS16 arm up to 5 years. (See Protocol Amendments in Section 5.3.1.12 of this review.)

A Type B Pre-NDA Meeting was held on July 28, 2011 to discuss the format and content of NDA 203159 for LCS12 (Skyla). During the discussion, the Division made the following comments:

- Pregnancies dated within 7 days after removal of the LCS12 should be counted as "on-treatment" pregnancies, to account for the margin of error in ultrasound dating.
- Bayer agreed to provide narratives for the pregnancies in the seven day window after removal.
- Bayer clarified that any pregnancies dated within three months after LCS removal would not be documented on case report forms but would be recorded on pregnancy forms and pregnancy outcome forms.
- Evaluation of efficacy will be based on the 12-month and cumulative 3-year unadjusted PI for women 18 to 35 years of age from the full analysis set (FAS) population of the phase 3 study. Bayer was also asked to provide unadjusted PIs for each year of use (e.g., 12-month, 24-month and 36-month). The Division agreed that it would be sufficient to provide analyses for women aged 18-35 and for the whole population, and to omit the PI for the small group of women aged ≥ 36 years.
- Total exposure for a subject should be expressed as the number of 28-day cycles, starting from insertion of LCS.

In Post-Meeting Comments, the Division requested the following:

- Bayer should submit the data expressed in 28-day cycle equivalents, as well as in the manner originally proposed (i.e., based on women-years, with the month(s) in which backup contraception was used to be subtracted). The 28-day cycle(s) where a concomitant contraceptive method was used should not be included in the total number of 28-day cycles for a subject. If a month in which back-up contraception was used spanned two or more 28-day cycles, the Division recommended that Bayer develop an algorithm to assign back-up to a single specific 28-day cycle equivalent in such cases.
- 28-day cycle equivalents would allow for consistency with other hormonal contraceptives in calculating the PI.
- The bleeding data should also be provided based on 28-day cycle equivalents, in the manner recommended by Mishell et al. (Contraception 2007, 75: 11-15).

Bayer responded to the Division's Post-Meeting comments above via an amendment to IND 73,505 (S-0048, submitted September 8, 2011). In that amendment, Bayer proposed to address the Division's Post-Meeting Comment as follows:

- Bayer agreed to provide 28-day cycle information datasets as proposed by the Division and to describe the algorithm used to assign back-up contraception use to specific 28-day cycles in the Statistical Analysis Plan for the Integrated Analysis.
- Bayer proposed to provide the unadjusted Year 1, Year 2, Year 3, and cumulative 3-year PI for the subgroup of women between 18 and 35 years of age based on this dataset as a sensitivity analysis as a part of the integrated analysis. The exposure would be calculated using all completed 28-day cycles in which no back-up contraception was used. Thirteen (13) cycles would constitute 1 woman-year.
- Bayer proposed to provide the bleeding data by 28-day reference periods in the same manner as the already planned analysis based on 30-day and 90-day reference periods. Bayer believed that the differentiation of bleeding events into scheduled and unscheduled bleedings, as proposed by Mishell et al, would require a cyclic regimen with hormone-free intervals and, therefore, could not be applied for LCS12.

In a November 22, 2011 Advice/Information Request letter, the Division communicated the acceptability of Bayer's proposals and, in addition, requested the following:

- The program files used to derive the 28-day cycle datasets and algorithm should be included in the NDA.
- The unadjusted Year 1, Year 2, Year 3, and cumulative 3-year PI analyses for the subgroup of women between 18 and 35 years of age based on the FDA-requested dataset should be presented independently for Study A52238.

On December 9, 2011, NDA 203159 was submitted for LCS12 for prevention of pregnancy for up to 3 years. The 3-year data for both LCS12 and LCS16 from protocols 310442 and 308901 (CSRs A52238 and A46796, respectively) were included in that NDA. On January 9, 2013, LCS12 was approved with the proprietary name Skyla. At the time of the Skyla NDA approval, the extension phase of protocol 310442 with LCS16 was ongoing.

Reviewer Comment

- *The Division's advice given for LCS12 (Skyla) was also intended to apply to the evaluation of LCS16.*

The extension phase of Protocol 310442 was subsequently completed and the 5-year safety and efficacy results for LCS16 were reported in CSR PH-37274; that report provides the pivotal 5-year safety and efficacy for LCS16.

A Pre-NDA Meeting was scheduled to be held on March 17, 2015. However, that meeting was cancelled at the Applicant's request on March 16, 2015 based on the FDA's preliminary responses of March 12, 2015 as well as the March 16, 2015 written feedback that Bayer received. NDA 208224 for LCS16 was submitted for review on November 18, 2015.

2.6 Other Relevant Background Information

2.6.1 Information Requests

2.6.2 Division of Medication Error Prevention and Analysis (DMEPA)

Proprietary Name Review
The proposed proprietary name, Kyleena, was reviewed by DMEPA on September 9, 2015 under IND 73505 and was found conditionally acceptable. In their final review dated February 17, 2016, DMEPA concluded that the proposed proprietary name is acceptable from both a promotional and safety perspective.

Use Risk Analysis, Label and Labeling Review
DBRUP also requested DMEPA to evaluate the labels and labeling for NDA 208224. Based upon their assessment of the risk hazard analysis submitted, they agreed with Applicant that a Human Factors validation study was not required. They also found the carton labeling and container label acceptable.

However, they identified one area within the insertion instructions that may be improved upon to promote the safe use of Kyleena. They suggested adding the statement "Check expiration date of Kyleena prior to initiating insertion" as the third bullet in the subsection "preparation for insertion" within Section 2.1 Insertion Instructions of the

prescribing information. This was suggested in order to mitigate the risk of insertion of expired product.

Reviewer Comment

- *This statement regarding checking the expiration date was also included in the most recent approved labeling of Skyla and will be added to the Kyleena labeling.*

2.6.3 Good Clinical Practice Assessment Branch, Office of Scientific Investigations

On February 5, 2016, the Division requested the Office of Scientific Investigations (OSI) to audit 3 preselected sites from the LCS16 Efficacy study to insure data integrity. One of these sites was in the US (Dr. Jeffrey Baker's Site 2411 in Idaho Falls, ID); one was in Chile (Dr. Maria Miranda's Site 1501) and one was in Hungary (Dr. Tamas Nyirady's Site 1806).

Dr. Baker's Site 2411 was selected for inspection because of its high enrollment. Numerous documentation discrepancies were noted in the subject records. These included:

- Subjects 241140, 246201, and 246221, all receiving LCS16 (16 µg/24 hrs), reported the use of concomitant contraceptives in their diaries, potentially affecting efficacy outcome; however, corresponding source documents indicated that no concomitant contraceptives were used during the respective time periods.
- Subjects 241140, 241197, and 246201 were administered laminaria at Visit 14 for cervical dilation; however, this concomitant medication was not reported.

Reviewer Comment

- *The use of laminaria was not a concern. Visit 14 was the final Month 60 study visit and the laminaria were most likely used to assist in the removal of the IUS.*

The final classification of these inspections was Voluntary Action Indicated (VAI) for the inspection of Site 2411 and No Action Indicated (NAI) for the inspections of Site 1501 and Site 1806.

Reviewer Comments

- *The LCS16 application utilized the same phase 3 clinical trial submitted to support the Skyla NDA application.*
- *At the time of the Skyla application, Bayer submitted an amendment to inform the Division of its decision to exclude one of the (US) Principal Investigators (Ronald Ackerman) from participating in the extension phase of the LCS16 Efficacy study due to compliance problems at the site (Site 2415). However, Bayer allowed this investigator to complete the 3 year phase of the study under "intensive*

monitoring." No pregnancies in either the LCS12 arm or the LCS16 arm were reported from this site.

- *At the same time, the Division received notification from Bayer that another (US) Principal Investigator (Richard Muckerman II) for the LCS Efficacy study (Site 2434) was implicated in fraudulent behavior related to this study. No pregnancies in either the LCS12 arm or the LCS16 arm were reported from this site.*
- *The FDA statistician performed a sensitivity analysis excluding these 2 sites (Site 2415 and Site 2434) from the efficacy calculations. She found that there were only minor changes on the estimate of pregnancy rates. The 1 year PI was 0.16 and 5-year cumulative pregnancy rate was 1.46 per 100 women.*

2.6.4 Center for Radiological Health (CDRH)

As mentioned earlier in this review, CDRH was consulted because the applicator (inserter) portion of the IUS is considered a device. Three specific CDRH consults were obtained.

1. CDRH was consulted regarding magnetic resonance imaging safety labeling information with LCS16, which contains a silver ring. The CDRH reviewer stated that the Applicant's MRI safety information in the proposed label was inconsistent with current practice and does not follow the recommendations found in the 2014 FDA Guidance for Industry entitled "Establishing Safety and Compatibility of Passive Implants in the Magnetic Resonance (MR) Environment." The CDRH reviewer provided the Applicant with acceptable labeling.

Reviewer Comment

- *Acceptable labeling regarding MRI safety was agreed upon by the Applicant and CDRH.*

2. A CDRH engineering review of the functionality of the LNG16 inserter was obtained. The functionality of the inserter was specifically evaluated through loading of the IUS and detachment force (the IUS must slide out of the inserter without significant peak forces). The inserter was evaluated at baseline, 3, 6, 9, and 12 months for several mechanical characteristics. The results of the studies demonstrated that the LCS16 inserter maintained its mechanical properties (breaking force minimum, recovery of horizontal arms, and inserter functionality) (b) (4)

Reviewer Comment

- *The results of this testing demonstrated that the LCS16 inserter maintained its mechanical properties and met all the CDRH acceptance criteria.*

3. The Division also requested that the Office of Compliance at CDRH evaluate the Applicant's compliance with applicable Quality System Requirements for the approvability of NDA 208224. As mentioned above, the consult request was for the inserter portion of the combination product, not the T-body portion of the product, which is considered the drug component. The inserter components are identical to the inserter used for the Skyla IUS with the exception of the gray colorant to the slider and flange and the blue color of the threads.

Reviewer Comments

- *The Quality System Requirements showed no deficiencies.*
- *The CDRH Office of Compliance reviewer concluded that LCS16 is approvable from the perspective of the applicable Quality System Requirements.*

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

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

3.2 Compliance with Good Clinical Practices

The Applicant attests that the pivotal phase 3 clinical trial and the supportive phase 2 clinical trial were conducted in compliance with Good Clinical Practice. See Section 2.6.3 regarding the Applicant's termination of two investigators from the phase 3 study.

3.3 Financial Disclosures

Bayer submitted a signed Certification: Financial Interests and Arrangements of Clinical Investigators form (Form FDA 3454) in compliance with 21 CFR part 54 for the pivotal LCS16 Efficacy study, Protocol 91665/310442. [Protocol 91665 was for the original 3-year portion of the phase 3 study and Protocol 310442 was for the 2-Year extension of that study.]

Financial Disclosure information for the 3-year part of the LCS16 efficacy study was provided in the Skyla NDA. The current submission includes financial disclosure Information covering the full 5-year period of the study plus 1 year following the completion of the study.

All investigators and sub-investigators in the phase 2 Study A46796 filed Financial Certification/Disclosure Forms and all marked "No" under Disclosable Information.

For the LCS16 efficacy study, all the investigators/sub-investigators filed a Financial Certification/Disclosure form with the exception of two physicians:

- [redacted], M.D. (Study Site [redacted]) did not participate in the conduct of the study.
- [redacted], M.D. (Study Site [redacted].) was never delegated any responsibilities in the study.

Only two physicians in Protocol [redacted] marked "Yes" under Disclosable Information.

- Dr. [redacted] was a principal investigator and coordinating investigator for the [redacted] study. Dr. [redacted] is located at the [redacted] The site recruited [redacted] subjects or [redacted]% of the total population enrolled. Out of the [redacted] subjects, [redacted] were screen failures, [redacted] entered treatment, [redacted] dropped treatment, [redacted] completed treatment, and [redacted] continued treatment in the extension phase of the study. Dr. [redacted] reported having received $191,800.00 for honoraria from Bayer for research grants, promotional talks on both oral contraceptives and intrauterine products, and serving on advisory boards. These honoraria covered the period of January 2008 through October 2011.
- Dr. [redacted] was also a principal investigator and coordinating investigator for the [redacted] study. Dr. [redacted] is located at the [redacted]. The site recruited [redacted] subjects or [redacted]% of the total population enrolled. Out of the [redacted] subjects, [redacted] were screen failures [redacted] entered treatment [redacted] dropped treatment, and [redacted] completed treatment. Dr. [redacted] provided financial disclosure information and reported having received $278,307.99 for honoraria from Bayer for research grants, promotional talks on both oral contraceptives and intrauterine products, and serving on advisory boards. These honoraria covered the period of January 2008 through October 2011.

Reviewer Comment

- *The potential for [redacted] financial arrangements to bias the study finding is minimal as their sites enrolled a total of [redacted] subjects or [redacted]% of the total study population of 2,885 subjects.*

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls (ONDQA)

ONDQA/Biopharmaceutics
The ONDQA/Biopharmaceutics team has reviewed the submitted data and has recommended approval from the Biopharmaceutics perspective.

ONDQA/Drug Product
The NDA was recommended for approval from the Drug Product perspective.

ONDQA/Drug Product Manufacturing Process
The Quality Assessment review was completed on August 4, 2016. The reviewer stated that the Applicant has adequately addressed all the information requests and that this NDA is recommended for approval from the perspective of the Drug Product Manufacturing Process.

ONDQA/Facilities
The ONDQA reviewer stated "There appear to be no significant or outstanding risks to the manufacturing process or final product based on the individual and composite evaluation of the listed facilities' inspectional history, relevant experience, and capabilities. The facilities are determined acceptable to support approval of NDA 208224."

Reviewer Comment

- *The Office of Combination Products concluded their review by stating;*

  "The application LCS16 (Levonorgestrel-releasing intrauterine system) 19.5 mg – NDA 208224 is approvable from the perspective of the applicable Quality System Requirements.

  (1) The documentation review of the application for compliance with the Quality System Requirements showed no deficiencies.

  (2) The recommended inspection(s) were conducted and deemed acceptable."

4.2 Clinical Microbiology

The Product Quality Microbiology Review was completed on June 14, 2016. From the product quality microbiology perspective, approval was recommended.

4.3 Preclinical Pharmacology/Toxicology

The Pharm/Tox reviewer in his review dated August 2, 2016 stated the following:

- Levonorgestrel has been extensively used as an approved product in a variety of oral contraceptives, hormone replacement therapy and LNG-releasing intrauterine systems, and its pharmacology is well known.
- Except for the removal thread and the flange of the inserter, the components of LCS16 IUS and body-contact components of the inserter are the same as those approved for use with Skyla (NDA 203159), including T-body core elastomer, membrane elastomer, silver ring, and the insertion tube of the inserter.
- The results of the biocompatibility tests indicate that the new LCS16 components are well-tolerated locally and systemically, were biocompatible under the conditions of the tests employed, and were not mutagenic.

The Pharm/Tox reviewer concluded that nonclinical data support approval of LCS16, levonorgestrel intrauterine delivery system 19.5 mg, for the prevention of pregnancy for up to 5 years.

4.4 Clinical Pharmacology

In her review dated 8/19/2016, the Clinical Pharmacology reviewer concluded that the clinical pharmacology information in the submission is acceptable to support the approval and for inclusion in the product labeling.

4.4.1 Mechanism of Action

The mode of action of all non-hormonal IUDs occurs mainly in the endometrial cavity due to the general reaction of the endometrium to a foreign body, which produces an environment that is spermicidal. This reaction consists of a sterile inflammatory response that produces tissue injury of a minor degree but sufficient enough to be spermicidal. The mode of action of LCS16 is mainly via its local progestogenic effects within the uterine cavity and cervix. The high LNG concentration in the endometrium causes thinning and atrophy, which inhibits implantation. These histological changes in the endometrium as well as a weak local foreign body reaction are observed with use of LCS16. In addition, LCS16 thickens the cervical mucus, creating a barrier to sperm penetration. Changes to the local milieu of the uterus and fallopian tubes inhibit sperm mobility and function, also preventing fertilization.

4.4.2 Pharmacodynamics

LCS16 has local progestogenic effects on the endometrium and the cervix. The local LNG levels stimulate histologic changes in the endometrium which include stromal pseudodecidualization and glandular atrophy. In the cervix, the mucus becomes scanty, thick and viscid. LNG released from the LCS16 system is also rapidly absorbed into the systemic circulation and affects ovulation frequency in some women.

The serum LNG concentrations during the 5-year period of LCS16 use were generally not sufficient to suppress the hypothalamic-pituitary ovarian axis. Anovulation was rarely seen during the periods studied in women treated with LCS16. However, differences in ovulations between the 3 LNG doses (Mirena, Skyla and LCS16) were detectable. A higher frequency of anovulation was observed in women using Mirena (highest dose) compared to both of the lower-dosed treatments. See Section 6.1.4.1 and Section 6.1.4.2 regarding the ovarian function substudies.

4.4.3 Pharmacokinetics

The pharmacokinetic (PK) characterization of LCS16 is based on data obtained from the phase 2 and phases 3 clinical studies. No clinical pharmacology studies were submitted to the NDA.

LCS16 was designed to have an initial *in vitro* LNG release rate of 16 µg/day. The *in vivo* release rate is approximately 14.9 µg/day in Weeks 3 to 4 and is reduced to approximately 7.4 µg/day after five years. The mean LNG *in vivo* release rate is approximately 19.6 µg/24 hours over the period of three years. Mirena, which is approved for up to 5 years of use, has an initial *in vitro* release rate is 20 µg of LNG daily, declining to 10 to 14 µg per day after five years.

Table 1 Pharmacokinetics of LCS12, LCS16 and Mirena

Parameter	LCS16 NDA 208224	Skyla NDA 203159	Mirena NDA 021225
Total LNG content	**19.5 mg**	13.5 mg	52 mg
Dimensions horizontal x vertical width of T-body (mm)	**28 x 30**	28 x 30	32 x 32
Insertion tube outer diameter (mm)	**3.8**	3.8	(b) (4)
Drug reservoir diameter/length (mm)	**2.8/** (b) (4)	2.8/ (b) (4)	3.6/19
Initial *in vitro* LNG release rate	**16 µg/day**	12 µg/day	20 µg/day
Early release: Week 3-4 *in vivo* LNG release rate	**14.9 µg/day**	10 µg/day	-
Average *in vivo* LNG release rate over 3 years	**9.6 µg/day**	6.4 µg/day	-
Average *In vivo* LNG release rate at the end of 3 years (Skyla) and 5 years (**LCS16**, Mirena)	**7.4 µg/day**	4.8 µg/day	15 µg/day

Source: Adapted from CSR A52238, Page 17, Table 7-1 and Amended CSR A52238

Reviewer Comments

- *The T-body dimensions and the silver ring are the same as Skyla's. The main physical difference between Skyla and the LCS16 is the length of the drug reservoir* (b) (4) *The different lengths result in the different LNG release rates. Skyla contains 13.5 mg of LNG and has an initial in vitro release rate of 12 µg of LNG per day. LCS16 contains 19.5 mg of LNG and has an initial in vitro release rate of 16 µg of LNG per day.*
- *Skyla and the LCS16 IUSs are smaller in dimensions (i.e., 28 x 30 mm) than Mirena (32 x 32 mm). Also, the insertion tubes used for Skyla and LCS16 are thinner (diameter 3.8 mm) than the one used in the Mirena pivotal studies (* (b) (4) *mm).*

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

NDA 208224 consists of one phase 3 primary clinical trial and one phase 2 supportive trial. All trials were conducted under IND 73,505.

The phase 3 primary clinical trial (CSR PH-37274, Protocol 91665/310442) is entitled "Multi-center, open-label, randomized study to assess the safety and contraceptive efficacy of two doses (*in vitro* 12 µg/24 h and 16 µg/24 h) of the ultra-low dose levonorgestrel contraceptive intrauterine systems (LCS) for a maximum of 3 years in women 18 to 35 years of age and an extension phase of the 16 µg/24 h dose group (LCS16 arm) up to 5 years." The study was conducted at sites in Europe, North America, and South America between 2007 and 2013.

Reviewer Comments

- *The LCS16 5-year trial is a 2-year extension of the 3-year phase 3 Study A46796 that was submitted to support the Skyla approval.*
- *Based on earlier agreements with Bayer, the evaluation of LCS16's efficacy will be based on the 12-month and cumulative 5-year unadjusted PI for women 18 to 35 years of age from the FAS population of the phase 3 study only.*

The phase 2 supportive trial (CSR A46796, Protocol 308901) is entitled "Multi-center, open, randomized, dose finding phase II study to investigate for a maximum of three years ultra-low dose levonorgestrel contraceptive intrauterine systems (LCS) releasing *in vitro* 12 µg/24 h and 16 µg/24 h of levonorgestrel compared to Mirena in nulliparous and parous women in need of contraception." Study A46796 was conducted at sites in 5 European countries (Finland, Hungary, Norway, Sweden and the United Kingdom) between 2005 and 2008.

Reviewer Comments

- *In this review, the phase 3 study (CSR PH-37274, Protocol 91665/310442) will generally be referred to as the "the LCS16 efficacy study" and the phase 2 trial (CSR A46796, protocol 308901) will be referred to as "the phase 2 study."*
- *CSR PH-37274 provides efficacy and safety results for LCS16 over the whole treatment period. The 3-year efficacy and safety results comparing LCS16 and LCS12 are found in CSR A52238.*

Table 2 Completed Clinical Trials

Protocol Study Number	Design	Study population	Number of women by treatment group	Main outcomes
The Phase 3 LCS16 5-Year Efficacy Trial				
Protocol: 91665/310442 **CSR: PH-37274** -11 countries (Europe, US, Canada, South America) -138 study centers -August 20, 2007 to June 7, 2013	-3 year multicenter, randomized, open label, 2-arm, parallel group - 2 year extension for single-arm LCS16 only	- Healthy -18 to 35 years -Nulliparous or parous women	Randomized=2885 FAS = 2884 **LCS12** -FAS = 1432 -Completed = 819 -Mean treatment duration: 821 days or 2.25 WY **LCS16** -FAS = 1452 -Completed = 870 -Mean treatment duration: 843 days or 2.31 WY **LCS16 extension phase** -FAS = 707 -Completed = 550	-Pregnancy rate -Bleeding pattern -Safety
The Phase 2 Study				
Protocol: 308901 **CSR: A46796** -5 countries in Europe -37 study centers -April 19, 2005 to December 9, 2008	-3 year multicenter, randomized, open label, controlled, 3-arm, parallel group	-Healthy -21 to 40* years -Nulliparous or parous women	Randomized=742 FAS = 738 **LCS12** -FAS = 239 -Mean duration of treatment: 915 days or 2.51 WY **LCS16** -FAS = 245 -Mean treatment duration: 912 days or 2.50 WY **Mirena** -FAS = 254 -Mean treatment duration: 895 days or 2.45 WY	-Pregnancy rate -Bleeding pattern -Safety

*Actual age range was 20 to 41 years due to the inclusion of a woman with an age above the inclusion criteria age range.
Source: Adapted from Module 2.7.6 Synopses of Individual Studies

Reviewer Comment

- *The two studies differ in several ways. These differences will be discussed later in the review.*

5.2 Review Strategy

There were several protocols and clinical study reports (CSRs) submitted with this NDA application.

- For Protocol 91665/310442:
  - CSR PH-37274 reports the 5-year results of the LCS16 IUS group (the LCS16 Efficacy study)
  - CSR A52238 reports the 3-year results of LCS12 and LCS16 groups.
- For Protocol 308901:
  - CSR A46796 reports the phase 2 study results

The 5-year LCS16 efficacy study as well as the 3-year supportive phase 2 study were both reviewed to assess the safety and efficacy of LCS16. Efficacy was assessed using only the LCS16 efficacy study. The phase 2 study was supportive. Safety was assessed using the pooled data from both studies.

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 Primary Clinical Trial (CSR PH-37274, Protocol 91665/310442)

5.3.1.1 Study Title

The title of the phase 3 primary study is a "Multi-center, open-label, randomized study to assess the safety and contraceptive efficacy of two doses (in vitro 12 µg/24 h and 16 µg/24 h) of the ultra-low dose levonorgestrel contraceptive intrauterine systems (LCS) for a maximum of 3 years in women 18 to 35 years of age and an extension phase of the 16 µg/24 h dose group (LCS16 arm) up to 5 years."

Reviewer Comment

- *The intrauterine systems (LCS12 and LCS16) used in this study did not utilize the to-be-marketed* (b) (4) *inserter. This is further discussed in Section 7.3.5 of this review.*

5.3.1.2 Study Objectives

The objectives of this study were to assess the safety, efficacy and pharmacokinetics of the two doses of the LCS12 and LCS16 (initial *in vitro* release rates of 12 µg and 16 µg per day, respectively), in women 18 to 35 years of age for up to 3 years. The LCS16 treatment arm was studied for up to 5 years by including a 2-year extension study.

5.3.1.3 Clinical Trial Design

The trial was conducted at 138 study sites in 11 countries in Europe, Latin America, the US and Canada. A total of 109 of the study sites participated in the 2-year extension phase of the study.

The women in the study were between 18 and 35 years of age, in good general health, and in need of contraception. A total of 3,661 women were screened for participation in the study, leading to a total of 2,885 women who were randomized. Both nulliparous and multiparous women were enrolled. The full analysis cohort (FAS) was used for all efficacy and safety analyses. The FAS was defined as including all women for whom the IUS was inserted or the insertion of an IUS was attempted. One subject was randomized to the LCS16 group but no insertion was attempted and so she was excluded from the FAS. A total of 1,432 subjects were randomized to receive LCS12 and a total of 1,452 women were randomized to the LCS16 cohort.

5.3.1.4 Clinical Trial Sites

The study was conducted at 138 centers in 11 countries. The principal investigator at each center was responsible for the conduct of the study. Only physicians qualified by training and experience to perform the LNG-IUS insertions were used as investigators.

A total of 109 of the study sites participated in the 2-year extension phase of the study.

Table 3 Number of LCS-treated Subjects by Country, LCS16 Efficacy Study

Countries	Study Sites	Enrollment	Randomized to LCS16	FAS[1]	Subjects who completed 3 years	Subjects in Extension
USA	57	1,543	564	563	268	198
Finland	15	589	261	261*	179	153
Canada	13	235	92	92	63	49
Sweden	11	219	90	90	58	53
Netherlands	9	199	83	83	51	36
Hungary	8	336	149	149	102	97
France	8	47	21	21	14	10
Norway	5	95	41	41	26	20
Argentina	5	169	72	72	58	48
Mexico	4	131	42	42	26	19
Chile	3	98	38	38	25	24

[1] Full Analysis defined as all women for whom the IUS was inserted or the insertion of an IUS was attempted.
*Included 6 subjects in the pharmacokinetic analysis set
Source: Amended CSR PH-37274, Page 65, Table 8-1

5.3.1.5 Inclusion Criteria

1. Has signed informed consent.
2. Is between 18 and 35 years (inclusive), in good general health and requesting contraception.
3. Has, in the opinion of the investigator, suitable general and uterine conditions for inserting the LCS.
4. Has clinically normal safety laboratory results (i.e., inside the specified range for inclusion).
5. Is willing and able to attend the scheduled visits and to comply with the study procedures.
6. Has regular menstrual cycles (length of cycle 21-35 days) (i.e., endogenous cyclicity without hormonal contraceptive use).

5.3.1.6 Exclusion Criteria

1. Known or suspected pregnancy or is lactating.
2. Vaginal delivery, cesarean delivery, or abortion within six weeks prior to Visit 1. Note: Postpartum insertions should be postponed until uterus is fully involuted, however, not earlier than six weeks after delivery. If involution is substantially delayed, consider waiting until 12 weeks postpartum. In case of a difficult insertion and/or exceptional pain or bleeding during or after insertion, physical examination and ultrasound should be performed immediately to exclude perforation.
3. History of ectopic pregnancies.
4. Infected abortion or postpartum endometritis within three months prior to visit 1.
5. Abnormal uterine bleeding of unknown origin.
6. Any genital infection (until successfully treated).
7. Abnormal cervical smear result
8. History of, or current, pelvic inflammatory disease.
9. Congenital or acquired uterine anomaly.
10. Any distortion of the uterine cavity (e.g., by fibroids) likely to cause problems (in the opinion of the investigator) during insertion, retention or removal of the LCS.
11. History of, diagnosed or suspected genital malignancy, and untreated cervical dysplasia.
12. Current deep venous thrombosis or thrombophlebitis; history of deep venous thrombosis.
13. Clinically significant endometrial polyp(s) which, in the opinion of the investigator, will interfere with the assessment of the bleeding profile during the study.

14. Clinically significant ovarian cyst(s).

15. Concomitant use of other sex-hormone containing preparations or intrauterine devices.

16. Use of any long-acting injectable sex-hormone preparations within 12 months prior to start of study medication, and if entering subset 2 or subset 3: any sex-hormone administration within one month prior to start of the study medication.

17. If entering Subset 2: any drug that might affect the blood coagulation (e.g., heparin, coumarin) within one month prior to start of the study medication.

18. If entering Subset 2: any known condition that might affect the blood coagulation.

19. Established immunodeficiency.

20. Any known hypersensitivity to the constituents of the LCS.

21. Diagnosed or suspected malignant or premalignant disease at the screening.

22. Arterial hypertension not responding to treatment, with systolic pressure > 140 mm Hg or diastolic pressure > 90 mm Hg.

23. Current (or history of) severe hepatic diseases including benign or malignant tumors. There should be an interval of at least three months between the return of liver function values to normal and the start of study treatment (i.e., LCS insertion).

24. History of chronic alcoholism, drug dependence or abuse, psychotic states or severe neurosis or any other condition that, by judgment of the investigator, might impair subject's ability to cooperate.

25. Known or suspected HIV infection or high risk for sexually transmitted disease (STD).

26. Any clinically significant condition or laboratory result that, in the opinion of the investigator, compromises subject’s safety, or might interfere with the evaluations or prevent the completion of the study. Non-inclusion laboratory values will be flagged by the laboratory based on predefined ranges.

27. Participated in another clinical study or consumed another experimental drug within one month prior to visit 1.

28. Previous participation in this study.

29. A person with close affiliation with the investigational site; e.g., close relative of the investigator, dependent person, employee or student of the investigational site.

30. Hungary only: Nulliparous

Reviewer Comment

- *Exclusion criterion #2 is in accord with current Skyla and Mirena labeling.*

5.3.1.7 Concomitant Therapy

Concomitant therapy was defined as all medication used up to 1 month before the screening visit, during the screening period, and during the treatment period. All concomitant medication used during study treatment was to be reported on the CRF. All concomitant medications were reported on the CRF as follows: brand name of the medication, indication, dose, frequency, route of administration and start and stop dates.

Prior and concomitant therapy that was not allowed before or during the study are defined in the exclusion criteria (Criteria 15, 16, 17 and 27) found in Section 5.3.1.6. When LCS removal was scheduled (at premature discontinuation/end of the study visit), the subject was to start using a condom or another barrier method of contraception at least 7 days before LCS removal, unless the removal was to take place during the first 7 days of menstruation.

If the LCS had to be removed without prior scheduling or the subject did not use condom or another barrier method as instructed, post-coital contraception was to be considered if intercourse had taken place.

The only concomitant contraception allowed was a barrier method, e.g. condoms to prevent STD.

Reviewer Comments

- *During study treatment, subjects were to be asked about the use of any concomitant contraceptive methods and these were to be recorded on the diary on a monthly basis. In the event of documented use of a concomitant contraceptive method, the period of additional contraceptive method use was excluded from the exposure time as defined in the SAP.*
- *Approximately 80% of the women treated with LCS16 did not use back-up contraception at all during the treatment years 1-5. In each year, less than 1% of women used back-up contraception for a total of 6 months or more.*

5.3.1.8 Study Procedures

Scheduled Visits

There were 10 scheduled study visits: screening (Visit 1), baseline (Visit 2), seven interim visits (Visits 3-9) and the end of study visit (Visit 10). A serum pregnancy test was obtained at screening, baseline, and at the end of the study (Visits 1 and 10), and at any interim visits if pregnancy was suspected. See Appendix-1 Schedule of Assessments/Events.

Screening Visit (Visit 1):
Informed Consent was obtained.

Baseline Visit (Visit 2):
The baseline visit usually occurred two to four weeks after the screening visit. A pregnancy test was performed. The LCS was inserted at the baseline visit within seven days after the onset of a menstrual period or when the subject was considered eligible for participation if she was using a hormonal contraceptive method or a non-hormonal IUD. The use of local anesthesia, dilatation or oral painkillers was permitted. Two insertion attempts were permitted per subject. If the second attempt failed, the subject was withdrawn from the study. If the LCS became unsterile before the insertion, or the inserter malfunctioned, a new LCS was used. Any LCS taken from the blister but not inserted successfully was stored appropriately until returned to the Applicant. If the LCS was successfully inserted but later partially or totally expelled or a uterine perforation occurred; the subject was withdrawn from the study.

Reviewer Comment

- *LCS expulsion was reported as an adverse event (AE); uterine perforation was reported as a serious AE (SAE).*

When the LCS removal was scheduled (at premature discontinuation/end of the study visit), the subject was instructed to start using condoms or another barrier method for contraception at least seven days before LCS removal, unless the removal took place during the first days of menstruation.

Withdrawal of Subjects from the Study
The following criteria were used to withdraw a subject from the study:
1. Pregnancy
2. After two failed LCS insertion attempts at Visit 2
3. Complete or partial expulsion of the LCS (after a successful insertion)
4. Partial or total perforation of the uterus or cervix by the LCS
5. Pelvic inflammatory disease
6. Persisting ovarian cyst with diameter > 5 cm for 3 months or longer
7. Genital malignancy
8. Liver tumor
9. Allergic reaction to the study medication

10. Non-attendance of visits (i.e., if a subject did not attend 2 consecutive scheduled visits without a major reason).

Interim Visits (Visits 3-9):

At the interim Visits 3 (3 months), 4 (6 months), 5 (9 months), 6 (12 months), 7 (18 months), 8 (24 months), and 9 (30 months), one blood sample was obtained per subject for the assessment of LNG and sex hormone binding globulin (SHBG).

End of Study Visit (Visit 10):

A blood sample for LNG and SHBG was obtained, the LCS was removed and future contraception was discussed with the subject.

For subjects entering the extension study (Visits 11 to 14), a schedule of study assessments can be found in Appendix 2.

Additional variables were studied in four subsets in preselected centers.

- Subset 1:
  - Ovarian and cervical function was studied in 40 subjects (20 per treatment arm) twice a week during a six week period in each study year.
- Subsets 2A and 2B:
  - 2A: Endometrial histology was studied in 60 subjects (30 per treatment arm).
  - 2B: Assessment of hemostatic factors was also assessed in the same 60 subjects.
  - Subsets 2A and 2B consisted of the same subjects.
- Subset 3:
  - Detailed PK of serum LNG and SHBG was determined in 24 subjects (12 per treatment arm) at baseline and at Days 1, 3, 7, and 14 after the start of treatment and at every subsequent visit.
- Subset 4:
  - Bone mineral density (BMD) was determined in 200 subjects (100 per treatment arm) at baseline and compared with measurements at Month 12, Month 24, Month 36/End of Study, Month 48 and at the end of the extension study.
  - BMD was assessed by dual x-ray absorptiometry (DXA) at the lumbar spine and total hip.

5.3.1.9 Primary Efficacy Variables

The primary efficacy variable was the number of unintended pregnancies during treatment measured by the PI with 2-sided 95% confidence intervals (CI); a secondary analysis used the life-table analysis (Kaplan-Meier method).

The FAS comprised all 2884 women who had at least one successful or unsuccessful insertion attempt (LCS12: 1432 women, LCS16: 1452 women). All safety and efficacy evaluations were also conducted on the FAS.

Reviewer Comment

- *In this study, all subjects who had successful and unsuccessful insertions were included in the FAS.*

A serum pregnancy test was performed at the screening visit. A urine pregnancy test was performed by the subjects at home on the morning of the baseline (treatment allocation) visit. A negative urine pregnancy test result at baseline was a requirement prior to LCS insertion. Women were then provided with home pregnancy tests to use as needed. A urine pregnancy test using a dipstick kit provided by the central laboratory was also performed at the end of study visit (Visit 10), i.e.; on the day when the LCS was removed.

Reviewer Comments

- *In both the Phase 2 study and the LCS16 Efficacy study, serum HCG testing was replaced by a urine pregnancy test at the end of study visit so that the test result was available before the IUS removal. This was implemented by Amendment in both studies.*
- *In the LCS16 Efficacy study, women performed home pregnancy tests as needed. The definition of "as needed" was not specifically defined in the protocol. In the Phase 2 study, women were asked to perform pregnancy tests on a monthly basis and record the results in their bleeding diary.*

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

The PI was defined as the number of pregnancies conceived on treatment or within 7 days after the LCS removal per 100 woman-years. PIs were obtained for each individual year of treatment, and cumulatively.

Unadjusted and adjusted PIs were calculated.

- The unadjusted PI included pregnancies that occurred during the exposure time ending with removal or partial or total expulsion of the LCS.
- For the adjusted PI, only the exposure time until the IUD was last known to be *in situ* or displaced within the uterine cavity was considered.

Reviewer Comments

- *Pregnancies that occurred after partial expulsion but before the IUS was removed were counted in the unadjusted PIs but would not have been counted in the adjusted PI calculation. There were no cases like this in either of the two studies.*
- *To determine efficacy, this review will focus on the unadjusted Year 1 Pearl Index and the unadjusted cumulative failure rate (Kaplan-Meier method) over 5 years.*

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

During the study, possible use of concomitant contraceptive methods was queried at each study visit and recorded on the subject's diary by the investigator on a monthly basis. (See Section 5.3.1.10 regarding the bleeding diaries.) In the event of documented use of a concomitant contraceptive method (e.g., condoms to prevent STD, or any excluded hormonal preparations), the period (in terms of calendar months, as documented on the diary page) of additional contraceptive use was excluded from the exposure time. All subjects were instructed to use condoms for contraception starting at least 7 days before LCS removal, unless the removal was to take place during the first 7 days of the menses. Therefore, the week before removal of the LCS was subtracted from the exposure for all subjects.

The formula used for the PI calculations was: PI = X/E where X = number of pregnancies and E = exposure time in 100 woman-years (one woman-year is 365 days of treatment exposure).

Reviewer Comments

- *Exposure data was given as woman-years (WY) based on individual exposure in terms of days of treatment. A total of 365 days was equal to one woman-year.*
- *The Division requested additional PI calculations be done based on 28-day cycle exposure data (1 WY equals 13 cycles), with back-up contraception subtracted in terms of 28-day cycles.*

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

5.3.1.10 Secondary Efficacy Variables

Bleeding

Secondary efficacy variables included assessments of bleeding patterns and intensity as recorded daily in subject-kept diaries. Subjects were instructed on how to use the diary and told to bring it to each study visit.

A reference period of 90 days was originally used to present bleeding events. The first reference period started on the day of insertion. For bleeding data collected during the first 360 days of treatment, the analysis was also presented for 30-day reference periods. For missing diary entries; the missing bleeding intensity was to be replaced by the maximum of the bleeding intensities of the day before and after the missing day. Up to five non-consecutive days per 90-day reference period could be replaced. Consecutive days with missing data were not replaced. In this case and if more than 5 non-consecutive days were missed, the entire period was considered missing for the analyses. A diary that ended before the end of the reference period was still evaluated if its length was at least 60 days, which is two-thirds of the 90-day reference period. The bleeding pattern indices incorporating the number of days or the number of events were corrected to account for the shorter length of the diary. The correction factor was to be the length of the reference period (90 days) divided by the length of the diary.

Reviewer Comment

- *In addition to the 90-day cycle data, Bayer was requested to submit the safety and efficacy data expressed in 28-day cycle equivalents.*

The following definitions were used to describe the bleeding.

Table 4 Bleeding/Spotting Definitions, LCS16 Efficacy Study

Category	Definition	Intensity Code
No bleeding	No vaginal bleeding.	1
Spotting	Less than associated with normal menstruation relative to the subject's experience, with no need for sanitary protection (except for panty liners).	2
Light	Less than associated with normal menstruation relative to the subject's experience, with need for sanitary protection.	3
Normal	Like normal menstruation relative to the subject's experience.	4
Heavy	More than normal menstruation relative to the subject's experience.	5

Source: CSR PH-37274, Page 54, Table 7-5

Ovarian and Cervical Function (Subset 1)

Ovarian function was studied by determining serum concentrations of progesterone, in a subset of 19 women.

Hormone levels (estradiol and progesterone) were collected for the subjects in this subset twice a week for a 6-week period in the second half of each study year (Years 1-5). Ovulation was assessed (based on serum progesterone levels) for each subject by year. Values of ≥ 2.5 ng/mL and ≥ 3.0 ng/mL (based on literature review) were used to assess the occurrence of ovulation. Descriptive statistics were used to show the maximum and the average concentration of estradiol and progesterone by year.

Cervical function was evaluated by examining the amount of mucus, spinnbarkeit, and ferning. Cervical function was studied by examining the cervical mucus at the same time points at which the blood samples are taken to assess ovarian function. Information on cervical function (sub-scores for amount of mucus, spinnbarkeit, ferning) was calculated and analyzed descriptively.

Endometrial Histology (Subset 2A)
Endometrial histology was studied at baseline and once a year through Year 5 in a total of 29 subjects treated with LCS16. Specimens were examined by a blinded pathologist.

PK Analysis (Subset 3)
The PK analysis set consisted of a total of 6 subjects who completed the 3-year study and provided a 3-year LNG and SHBG sample. A blood sample for the determination of serum LNG and SHBG was collected one sample per subject at one of the Visits 3 through 10. Three of these subjects continued into the 2-year extension phase.

Serum levels of LNG and SHBG were monitored and evaluated to provide population PK. In addition, serum LNG and SHBG levels were determined upon removal of the LCS in all subjects discontinuing the study prematurely. Descriptive statistics were used to show the average concentration of LNG and SHBG by year.

In addition, the release of LNG from LCS16 was determined by means of *ex vivo* residual content analysis of used LCSs collected from 345 randomly selected subjects in the LCS12 treatment arm who completed the full 3 years of treatment. LCSs from all subjects discontinuing the study prematurely (regardless of the treatment arm) were also analyzed.

Other Outcomes
Other outcomes in this trial included the physicians' rating of ease of LNG-IUS placement and removal (''easy,'' ''slightly difficult,'' or ''very difficult'') and the subjects' rating of pain during LNG-IUS placement and removal (''none,'' ''mild,'' ''moderate,'' or ''severe''). Additional outcomes included the need for cervical dilatation, local anesthesia, or pain medication (physicians' discretion); dysmenorrhea (graded as none, mild, moderate, or severe); and adverse events and serious adverse events (including expulsion and uterine perforation).

5.3.1.11 Safety Data

The following safety parameters were monitored during the clinical trial:

- Adverse events (AEs), serious AEs (SAEs) presented using MedDRA (version 17.1)
- Concomitant medications
- The occurrence of dysmenorrhea
- Ease of LCS insertion and removal by the investigator
- LCS insertion/removal ease and pain by the subject
- The IUS expulsion and perforation rates
- The overall discontinuation rates
- Ectopic pregnancies
- The occurrence of pelvic inflammatory disease (PID)
- The occurrence of ovarian cysts (these were reported as AEs if they were abnormal non-functional cysts and/or had a diameter > 3 cm)
- Vital signs
- Physical and pelvic examinations, including vaginal and cervical smears and vaginal ultrasound
- Clinical laboratory tests
- Endometrial safety (subset only)
- Bone mineral density (subset only)

5.3.1.12 Protocol Amendments

The original protocol, dated June 28, 2007, was amended five times. Clinically significant amendments are listed below.

Amendment 1
Amendment 1 dated October 4, 2007 specified the following:

- This was a local amendment for Hungary only: An additional exclusion criterion was added in order to exclude nulliparous women.

Amendment 2
Amendment 2 dated January 27, 2008 made the following changes:

- The wording of Exclusion Criteria 7, 13 and 14 was revised, although the medical content of each criterion did not change.
- The pregnancy test at the end of the study was changed from a serum to a urine test, so that the result was available before removal of the LCS.
- The timelines for SAE and pregnancy reporting were changed to within 24 hours.
- In order to reflect medical practice in North America, the transvaginal ultrasound that was to be performed at screening was deleted.

Prior to implementation of this amendment, a total of 3,051 subjects had been screened and 2,125 subjects had been randomized for this study. Of these, a total of 1,175 subjects had been screened and 614 subjects had been randomized in the USA and Canada.

Amendment 3
Amendment 3 dated January 16, 2009 was implemented when all subjects had already been recruited. It specified the following global modifications:

- Compliant subjects were clarified as those in whom the LCS was correctly located in the fundal position (*in situ*) or in whom it was displaced but still in the uterine cavity (displace, intrauterine).
- A user satisfaction questionnaire was added to the end-of-study visit.
- The visit window of the premature termination examination was clarified.
- In Chile only, there was a change in the central laboratory.
- In Finland only, the serum samples collected for pharmacokinetic analysis in study subset 3 were to be analyzed additionally for silver ion concentration.

Amendment 4
Amendment 4 dated October 7, 2009 contained some administrative changes and a change of the central laboratory in the USA and Canada.

Amendment 5
Amendment 5 dated November 30, 2009 was implemented when all subjects had already been recruited. It specified the following global modifications:

- Treatment in the LCS16 treatment arm was extended up to 5 years. As a result of the study extension, the title of the study was changed to: "*Multi-center, open-label, randomized study to assess the safety and contraceptive efficacy of two doses (in vitro 12 µg/24 h and 16 µg/24 h) of the ultra-low dose levonorgestrel contraceptive intrauterine systems (LCS) for a maximum of 3 years in women 18 to 35 years of age and an extension phase of the 16 µg/24 h dose group (LCS16 arm) up to 5 years.*"

Amendment 6
Amendment 6 dated May 13, 2013 was implemented when all subjects had already been recruited. It specified the following global modification:

- The number of returned LCS16 devices that were to be analyzed for residual LNG content from subjects that completed the 5-year treatment was changed from all returned LCS16 devices to 345 LCS devices.

5.3.1.13 Protocol Deviations

Both major and minor protocol deviations were recorded in 1177 of the 1452 (81.1%) subjects enrolled in the LCS16 arm of the study. The most common protocol deviations included procedure deviations (61.1%) and time schedule deviations (53.0%).

A total of 26 subjects (1.8%) treated with LCS16 had at least one major protocol deviation. The major protocol deviations were all due to excluded concomitant treatment use, e.g., other sex hormone-containing preparation. Subject 200606 (in the no-extension group) was erroneously reported to have an inclusion/exclusion error at study entry.

Overall, there were more subjects with protocol deviation (major or minor) in the extension group than in the no-extension group due to the fact that they had a higher number of visits/examinations due to the longer study time.

Table 5 gives an overview of all protocol deviations.

Table 5 LCS16, Subjects Protocol Deviations, LCS16 Efficacy Study

	No-extension* N=745 (100%) n (%)	Extension N=707** (100%) n (%)	Total N=1452 (100%) n (%)
At Least One Protocol Deviation	573 (76.9)	604 (85.4)	1,177 (81.1)
At Least One Minor Protocol Deviation:	568 (76.2)	602 (85.1)	1,170 (80.6)
-Inclusion/exclusion error at study entry	34 (4.6)	26 (3.7)	60 (4.1)
-Randomization/ registration error	4 (0.5)	3 (0.4)	7 (0.5)
-Withdrawal criteria present but not withdrawn	3 (0.4)	2 (0.3)	5 (0.3)
-Excluded concomitant treatment	10 (1.3)	3 (0.4)	13 (0.9)
-Treatment deviation	44 (5.9)	28 (4.0)	72 (0.5)
-Time schedule deviation	300 (40.3)	470 (66.5)	770 (53.0)
-Procedure deviation	460 (61.7)	427 (60.4)	887 (61.1)
-Other	0	1 (0.1)	1 (<0.1)
At Least One Major Protocol Deviation	17 (2.3)	9 (1.3)	26 (1.8)
-Inclusion/exclusion error at study entry	1 (0.1)	0	1 (<0.1)
-Excluded concomitant treatment	17 (2.3)	9 (1.3)	26 (1.8)

N = Total number of LCS16-treated subjects (FAS=1,452)
*Number of LCS16 subjects in the FAS who did not enter into the extension phase.
**Number of LCS16 subjects in the FAS who entered the extension phase.
Source: CSR PH-37274, Page 70, Table 8-5 and Page 52 of 1210, Table 14.1

Reviewer Comments

- *It is unlikely that the above protocol violations affected the validity of the analysis.*
- *All subjects who were mistakenly given the LCS other than the one to which they were randomized were analyzed according to the actual treatment received.*

5.3.2 Supportive Clinical Trial (Study A46796, Protocol 308901)

5.3.2.1 Study Title

Study A46796 was a multicenter, open, randomized, dose-finding study entitled: "Multi-center, open, randomized, dose finding phase II study to investigate for a maximum of three years ultra-low dose levonorgestrel contraceptive intrauterine systems (LCS) releasing *in vitro* 12 µg/24 h and 16 µg/24 h of levonorgestrel compared to MIRENA in nulliparous and parous women in need of contraception."

Reviewer Comments

- *In this review, this study will be referred to as the phase 2 study.*
- *The to-be-marketed* (b) (4) *inserter was not utilized for this study. (See Section 7.3.5 regarding the to-be-marketed* (b) (4) *inserter.)*

The study was performed at 37 centers located in Finland, Hungary, Norway, Sweden, and the United Kingdom and enrolled parous and nulliparous women, 21 to 41 years of age and in good general health, who needed contraception. The FAS consisted of all subjects who underwent a successful IUS insertion.

The PI was the primary efficacy variable. A secondary analysis was performed using the Kaplan-Meier method.

Bleeding patterns were evaluated from bleeding data obtained from subject-kept diaries as secondary efficacy variables. Safety measurements were assessments of AEs, laboratory variables, physical and gynecological examinations, and vital signs. Other secondary variables measured in subsets of women were ovarian and cervical function, endometrial histology, and pharmacokinetic parameters. Other evaluations included ease and pain assessment on IUS insertion/removal, IUS expulsion rate, discontinuation rates, compliance, and return to fertility.

The study was conducted according to the final approved protocol, dated March 4, 2005 and its amendments 1 (dated November 24, 2005) and 2 (dated December 13, 2007). The study was conducted from April 19, 2005 to December 9, 2008. As noted in Table 6 below, there were some differences in the phase 2 LCS16 and the to-be-marketed LCS16.

Table 6 LCS16, Formulations in the Phase 2 and Phase 3 Studies

Component	Phase 2 Study	Phase 3 LCS Efficacy Study	LCS16 To-be-marketed Product
Drug Core LNG Content	(b) (4)	19.5 mg	19.5 mg
(b) (4) Drug Core-Length		19 mm	19 mm
To-be-marketed (b) (4) inserter utilized		(b) (4)	Yes

Source: Summary of Biopharmaceutics, Module 2.7.1, Page 11, Table 1-1

Reviewer Comments

- *There were some differences between the phase 2 and phase 3 studies in population and study design:*
  - *The women in the phase 3 LCS16 efficacy study were slightly younger (inclusion age 18 to 35 years) than those in the phase 2 study (inclusion age 21 to 40 years, actual age range: 20 to 41) and came from a broader geographic population (Europe, US, Canada, South America) than those in the phase 2 study (Europe only).*
  - *The LCS16 Efficacy study had a much larger population (2,884 women) than the phase 2 study (741 women). In the pooled LCS groups, 85.6% of women were from the phase 3 study (LCS12, 1432/1672; LCS16, 1452/1697). Therefore, the pooled analysis of the LCS groups is driven mainly by the LCS16 Efficacy study.*
  - *The LCS16 Efficacy study included a higher proportion of nulliparous women than the phase 2 study (39.2% vs. 21.5%).*
  - *In the phase 2 study, specific side effects classified as progestin-related (acne, bloating, breast pain, breast tension, edema, headache, mood changes, nausea and weight gain) were assessed at every visit via specific questioning. In contrast, these events were recorded as reported voluntarily by the women in the LCS16 Efficacy study. This difference in AE reporting may have led to a higher frequency of certain progestin-related side effects in the phase 2 study than in the LCS16 Efficacy Study.*
  - *In the LCS16 Efficacy study, the FAS was defined as including all women who had an attempted or successful IUS insertion. One subject who was randomized to the LCS16 group did not have an insertion attempt so was excluded from the FAS. In the phase 2 study, the FAS was defined as the set of subjects who had a successful insertion. Subjects with an unsuccessful insertion were not included in the FAS.*

(b) (4)

(b) (4)

- *Determination of product efficacy will be based only on the phase 3 trial as the LCS16 in this trial is identical to the to-be-marketed product in terms of drug content.*
- *Neither the phase 2 nor the phase 3 clinical trials utilized the to-be-marketed* (b) (4) *inserter.*

5.3.2.2 Study Objectives

The objective of this study was to identify an appropriate dose for a new LNG-IUS.

5.3.2.3 Clinical Trial Design, the Phase 2 Study

A total of 905 women between 21 and 41 years of age were screened, leading to a total of 742 who were randomized in a ratio of 1:1:1 and 738 who had an IUS inserted (LCS12: 239, LCS16: 245, Mirena: 254). All of the 738 women treated were included in the FAS, which was defined as the set of subjects who had a successful insertion. (Subjects with an unsuccessful insertion were not included in the FAS.) The FAS population was used both for the efficacy and safety analyses. There were no major protocol deviations. A total of 208 women (28.2%) discontinued the study prematurely.

The majority of women (733/738) in the FAS were Caucasian. The mean age of the subjects was approximately 32 years. The three treatment groups were comparable with respect to demographic and baseline characteristics. Of the 738 women, a total of 159 (21.5%) were nulliparous, and 579 (78.5%) had had one or more births. A total of 538 (72.8%) women had had at least one vaginal delivery. The treatment groups were also comparable with regard to gynecological history.

The study was single-blinded (blinded to the subjects but not to the investigators). It was not possible to blind the investigators because Mirena could be distinguished by its larger dimensions, and differences between LCS12 and LCS16 were apparent as the size of the hormone reservoirs was different.

Insertion of the IUS was followed by ultrasound to evaluate the placement. At the end of the three-year study, subjects in the Mirena group were given the option of continuing the IUS for up to 5 years.

Additional variables were studied in 3 subsets. All the subsets were studied in selected centers in Finland only.

The subsets were the following:

- Subset 1: Ovarian and cervical function studied in 60 subjects (20 per treatment arm)
- Subset 2: Endometrial histology studied in 90 subjects (30 per treatment arm)
- Subset 3: Pharmacokinetics studied in 37 subjects (12 per treatment arm)

5.3.2.4 Clinical Trial Sites, the Phase 2 Study

The study was conducted at 37 study centers in 5 countries. At each center, the principal investigator was responsible for the study. Only physicians qualified by training and experience to perform the LNG-IUS insertions were used as investigators.

5.3.2.5 Inclusion Criteria, the Phase 2 Study

The main criterion for inclusion in the study was parous or nulliparous women of 21 to 40 years of age who were in good general health and in need of contraception.

The following criteria were used to evaluate subjects for inclusion in the study:

1. Signed informed consent.
2. Parous or non-parous woman of 21 to 40 years of age (inclusive) with good general health and in need of contraception.
3. Normal size uterus (as measured with ultrasound). Uterine cavity considered suitable by the investigator for insertion of the IUS.
4. Clinically normal safety laboratory results (i.e., inside the specified range for inclusion)
5. Willingness and ability to attend the clinic for scheduled visits and to comply with the study procedures.
6. Regular menstrual cycles (length of cycle 21-35 days) (i.e., endogenous cyclicity without hormonal contraceptive use).

Reviewer Comments

- *Inclusion and exclusion criteria were mostly identical between the pivotal LCS16 Efficacy Study and the phase 2 Study.*
- *The age limit for study inclusion was higher than in the phase 3 study (which was 18 to 35 years inclusive).*
- *Although the inclusion criterion stated subjects must be between 21 to 40 years of age to be enrolled, the actual ages of enrolled study subjects were 20 to 41.*
- *Inclusion criteria included an ultrasound result indicating that the dimensions of the uterine cavity were suitable (investigators' discretion) for placement of an LNG-IUS of maximum dimensions 32 mm X 32 mm (Mirena).*

5.3.2.6 Exclusion Criteria, the Phase 2 Study

1. Known or suspected pregnancy or lactation.
2. End of last pregnancy; vaginal or cesarean delivery less than 12 weeks, or abortion within 12 weeks immediately before screening.
3. History of ectopic pregnancies.
4. Infected abortion or postpartum endometritis during the past 3 months.
5. Abnormal uterine bleeding of unknown origin.
6. Any genital infection (until successfully treated).
7. Descriptive diagnoses of epithelial cell atypias (not benign atypias) or more serious disorder in cervical smear (according to the Bethesda System) at screening and not responding to treatment.
8. History of or current pelvic inflammatory disease.
9. Congenital or acquired uterine anomaly.
10. Any distortion of the uterine cavity (for example, by fibroids) likely to cause problems during insertion, retention or removal of the IUS, in the opinion of the investigator.

11. History of, diagnosed or suspected genital malignancy, and untreated cervical dysplasia.
12. Previous or current climacteric symptoms.
13. Current endometrial polyps.
14. Ovarian cysts with diameter >3 cm.
15. Concomitant use of intrauterine device.
16. Any long-acting injectable sex-hormone preparations within six months prior to start of study medication, and if entering subset 3, then oral, implanted, transdermal, intrauterine or intravaginal sex hormone administration within one month prior to IUS insertion.

17. Established immunodeficiency.
18. Any known hypersensitivity to the constituents of the IUS.
19. Diagnosed or suspected malignant or premalignant disease.
20. Arterial hypertension not responding to treatment with systolic pressure >160 mmHg or diastolic pressure >95 mmHg after 5 minutes resting measured in sitting position.
21. Liver diseases: Presence or history of severe hepatic diseases including benign or malignant tumors. There should be an interval of at least 3 months between the return of liver function values to normal and the start of study medication intake.
22. History of chronic alcoholism, drug dependence or abuse, psychotic states or severe neurosis or any other condition that by judgment of the investigators might impair subjects' ability to cooperate.

23. Known or suspected HIV infection or high risk for sexually transmitted disease (STD).
24. Any clinically significant condition or laboratory result that, in the opinion of investigator, compromise subject safety, might interfere with the evaluations or prevent the completion of the trial.
25. Participation in another clinical trial within 1 month or intake of an experimental drug within 3 months prior to screening.

26. Previous assignment to treatment (e.g., randomization) during this study.
27. Close affiliation with the investigational site; e.g., close relative of the investigator, dependent person (e.g., employee or student of the investigational site).

28. Any concomitant medication within 1 month prior to start of study medication known or suspected to have potential of altering serum concentrations of levonorgestrel (e.g., primidone, barbiturates, phenytoin, carbamazepine, rifampicin, oxcarbamazepine and griseofulvin).

Reviewer Comments

- *Only parous women were enrolled in Hungary.*
- *An individual woman could enroll in only one of the above 2 clinical studies.*

5.3.2.7 Concomitant Therapy, the Phase 2 Study

Concomitant medication was taken by 593/738 women (80.4%; LCS12: 189 [79.1%], LCS16: 194 [79.2%], Mirena: 210 [82.7%]), with no notable differences among the treatment groups.

5.3.2.8 Study Procedures, the Phase 2 Study

Scheduled Visits
Study visits took place after inclusion at screening (Visit 1), at baseline for randomization and placement of the LNG-IUS (Visit 2), and at 1, 6, 12, 18, 24, 30, and 36 months after placement. A urine pregnancy test was obtained at baseline (Visit 2), and a serum pregnancy test was done at the end of the study (Visit 9). Subjects self-administered monthly urine pregnancy tests.

Screening Visit (Visit 1):
Informed Consent was obtained.

Baseline Visit (Visit 2):

A urine pregnancy test was performed and the LCS was inserted within seven days after the onset of a menstrual period or when the subject was considered eligible for participation if she was using a hormonal contraceptive method or a non-hormonal IUD.

Interim Visits (Visits 3-8):

Interim Visits included Visit 3 (Month 1 after placement), Visit 4 (6 months post-placement), Visit 5 (12 months post-placement), Visit 6 (18 months post-placement), Visit 7 (24 months post-placement), Visit 8 (30 months post-placement), and Visit 9 (36 months post-placement).

At each study visit, vital signs were evaluated and a gynecological examination, including vaginal ultrasound, was performed. Ultrasound assessments included checking the position of the LNG-IUS in the uterine cavity and measuring endometrial thickness and ovarian size. Subjects were also questioned about progestin-related adverse events (headache, nausea, mood changes, bloating, edema, skin effects [acne or greasy skin], breast pain/"tension," and weight gain) occurring in the month preceding each clinic visit.

5.3.2.9 Primary Efficacy Variables, the Phase 2 Study

The number of pregnancies was recorded and the pregnancy rate (PI) was calculated as the primary efficacy variable. The FAS was defined as the set of subjects who had a successful insertion. Subjects with an unsuccessful insertion were not included in the FAS.

5.3.2.10 Secondary Efficacy Variables, the Phase 2 Study

The secondary variables, number of IUS expulsions and discontinuations for bleeding problems, progestin-related side effects and overall discontinuations were recorded and their rate calculated. Bleeding patterns were evaluated from bleeding data obtained from subject-kept diaries. IUS insertion and removal ease and pain were evaluated by the subject (pain) and the investigator (ease). Occurrence of dysmenorrhea was assessed at every visit. Progestin-related side effects within the previous one month were assessed at every visit via specific questioning. All other adverse events were recorded as reported voluntarily by the subject or elicited.

Cumulative Failure Rates

The probability of getting pregnant using Kaplan-Meier estimates was calculated.

Bleeding

Subjects completed vaginal bleeding diaries on a daily basis. Bleeding outcomes were reported as the number and length of episodes, with bleeding graded as ‘‘none,’’

''spotting'' (no need of sanitary protection, or panty liners only), ''light'' (need of sanitary protection yet less than menstruation), ''normal,'' or ''heavy'' (more than normal menstruation according to the subjects' experience).

Ovarian and Cervical Function (Subset 1)

In subset 1, the ovarian and cervical functions were studied for 6 weeks in the latter half of each of the study years 1, 2 and 3. Ovarian function was studied by determining the serum hormone concentrations (progesterone and estradiol) twice a week during each 6-week period. Serum LNG and SHBG were also determined at these examinations. The cervical function was determined by examining the cervix/cervical mucus (using cervical score including spinnbarkeit and fern tests) at the same time points as the hormone concentrations were determined for the ovarian function (6 weeks each year, twice a week).

Endometrial Histology (Subset 2)

In subset 2, the endometrial histology was studied by a blinded pathologist reviewing annual endometrial biopsies (at baseline and after 1, 2 and 3 years of treatment). The endometrium was evaluated for descriptive histology and estrogen and progestin indices as well as for safety.

PK Analysis (Subset 3)

The PK of LNG was evaluated. Serum LNG and SHBG were determined at baseline and at Day 1, 3 and 7 and 2 weeks after start of treatment. Thereafter, they were determined at every visit.

Other Outcomes

Other outcomes included the physicians' rating of ease of LNG-IUS placement and removal (''easy,'' ''slightly difficult,'' or ''very difficult'') and the subjects' rating of pain during LNG-IUS placement and removal (''none,'' ''mild,'' ''moderate,'' or ''severe''). Additional outcomes included the need for cervical dilatation, local anesthesia, or pain medication (physicians' discretion); correct placement (defined as the presence of the LNG-IUS completely within the uterine cavity visualized by ultrasound); dysmenorrhea (graded as none, mild, moderate, or severe); adverse events and serious adverse events (including expulsion and uterine perforation).

A return to fertility questionnaire was sent out one year after the study was completed and also to all subjects who discontinued after the start of treatment.

5.3.2.11 Safety Data, the Phase 2 Study

Frequent pregnancy testing (once a month by the subject at home) was done throughout the study. One year after cessation of treatment, regardless of whether the subject discontinued prematurely or not, the return to fertility was assessed by a questionnaire.

Reviewer Comment

- *A blood sample for serum pregnancy test (for beta HCG) was taken at screening, at Visits 2, 10, 12 and 14 (end of extension), and at any interim visits if needed.*

All safety laboratory determinations were performed by a central laboratory, (b) (4) which also analyzed the progesterone and estrogen samples for subset 1. The LNG and SHBG analyses (Subset 3 and all patients at end of study) were done by (b) (4) and histological samples (Subset 2) were analyzed by (b) (4).

5.3.2.12 Protocol Amendments, the Phase 2 Study

The final study protocol, dated March 4, 2005, was amended twice. Significant sections of the amendments are listed below.

Amendment 1
Amendment 1, dated November 24, 2005, specified the following:

- Progestin-related side effects within the previous month were to be assessed at every visit via specific questioning and documented on a 'progestin-related side-effects' CRF page. In the original study protocol, progestin-related side-effects were also to be recorded as AEs. All other AEs were to be recorded as reported voluntarily by the subject or elicited.
- In order to avoid redundancy, only those progestin-related side-effects that were considered by the patient/investigator as AEs were to be transferred to the AE CRF page.

Amendment 2
Amendment 2, dated December 13, 2007, specified the following:

- The stopping rule was clarified to account for the two different experimental doses and the increasing exposure time.
- The withdrawal criterion with regard to ovarian cysts observed under treatment was modified to more closely reflect clinical practice. An ovarian cyst with a diameter > 5 cm, which had been confirmed by ultrasound and had not disappeared within 3 months, was considered a withdrawal criterion.
- End of Study pregnancy testing was changed from serum to urine

5.3.2.13 Protocol Deviations, the Phase 2 Study

A total of 2,080 protocol deviations were recorded for 597/738 women (80.9%). No protocol deviations were assessed as major and no deviations led to exclusion from the analyses. The majority of protocol deviations (57.9%) were procedure deviations; e.g., a condom was not used prior to removal of the IUS. The next most frequent (40.8%) were time schedule deviations; e.g., visits a few days early or late. and treatment

deviations (29.9%); e.g., the IUS used for less than 35 or more than 38 months.

6 Review of Efficacy

Efficacy Summary

One 5-year phase 3 clinical trial (Clinical Study Report PH-37274; Protocol 91665/310442; the "LCS16 Efficacy study") and one 3-year phase 2 clinical trial (Clinical Study Report A46796; Protocol 308901, the "Phase 2 study") have been submitted to the NDA to support the marketing claim of prevention of pregnancy for up to 5 years. Proof of efficacy of LCS16 is based on data from the 5-year phase 3 clinical trial. The primary efficacy variable was the number of unintended pregnancies during treatment and including those with the estimated date of conception within 7 days after the removal of the IUS, measured by the Pearl Index (PI) with 2-sided 95% confidence intervals (CI) and life-table analysis (Kaplan-Meier method). The PI was based on 28-day equivalent cycles and was defined as the number of pregnancies per 100 woman-years. Only unadjusted PIs were considered in the efficacy calculations.

Reviewer Comment

- *The differences between the unadjusted and adjusted PIs were in exposure time in case the IUS was expelled (total or partial). Pregnancies that occurred after the IUS was known not to be in situ or to be displaced in the uterus were not counted for the adjusted PI. The differences between the unadjusted and adjusted PIs were very small. For the purposes of determining LCS16 efficacy, only the unadjusted PIs were used.*

Based on the data from the 5-year phase 3 LCS16 Efficacy study, the PI of LCS16 for Year 1 was **0.16 (0.02, 0.58)**. The cumulative 5-year PI for LCS16 was 0.29 (0.16, 0.50).

The Kaplan-Meier estimate of the cumulative failure rate per 100 women for Year 1 was 0.18 (0.04, 0.71). The cumulative 5-year pregnancy rate by the Kaplan-Meier method was **1.45 (0.82, 2.53)**.

These PIs and life table analyses provide adequate evidence of the efficacy of LCS16 in the population targeted for marketing.

Reviewer Comments

- *In comparison, the Medical Officer's review of Mirena completed in December, 2000 documented that the PI for Mirena at 1 year was 0.19 (0.02, 0.70) and at 5 years was 0.08 (0.02, 0.23). The cumulative life table 5-year pregnancy rate reported in the current Mirena label is 0.7 per 100 women.*
- *Although cross-study comparisons are problematic, it would appear that LCS16 is similar to Mirena regarding efficacy.*

6.1 Indication

The Applicant's proposed indication for LCS16 is the prevention of pregnancy for up to 5 years.

6.1.1 Methods

Primary Analysis
The primary efficacy analysis for the approval of LCS16 is based on the LCS16 Efficacy study.

Reviewer Comments

- *By previous agreement with the Applicant, the Division required only one phase 3 clinical trial to obtain approval for this product. The contraceptive efficacy of LCS16 is therefore based on data obtained from the primary phase 3 LCS16 Efficacy study.*
- *Data from the smaller phase 2 study were reviewed for additional safety information.*

In the phase 3 study, a total of 2,885 women were randomized to either LCS16 (n=1,453) or LCS12 (n=1,432). An attempt to insert an LCS device was made in all but one subject. All randomized women in whom an insertion was at least attempted (N=2,884) were included in the FAS for this study.

The mean treatment duration (including extension) for LCS16–treated women was 1,160 days or 3.18 women-years (WY).

The FAS included 1,287 North American women, of whom 655 received LCS16 and 632 received LCS12. For the North American subset of the LCS16 group, this resulted in total exposure of 568 WY for the first treatment year (i.e., approximately 7,380 cycles of 28 days when 1 WY equals 13 cycles), 1,393 WY (i.e., approx. 18,100 cycles) over the 3-year treatment and 1,832 WY (or 23,800 cycles) over the entire 5-year treatment duration.

In the phase 2 study, a total of 742 women were randomized to treatment. Of these, a total of 741 women had a successful insertion attempted so were included in the FAS. A total of 738 women of the 741 (99.5%) had an LNG-IUS successfully placed. A total of 245 of the 246 women randomized to LCS16 had a successful IUS placement. The mean treatment duration was 912 days or 2.50 WY in the LCS16 group.

For both studies, contraceptive efficacy was based on the number of pregnancies that occurred during treatment or for which the estimated date of conception was within 7 days after IUS removal or detection of expulsion. The primary efficacy endpoint was the PI. Supportive Kaplan-Meier estimates of the cumulative pregnancy rate were also

calculated using total exposure time based on exposure days and based on 28-day cycles.

Secondary Analysis
In the phase 2 and the phase 3 studies, the secondary analysis was the cumulative failure rate calculated using the Kaplan-Meier method. Other secondary analyses were descriptive bleeding data, treatment compliance, return to fertility and user satisfaction.

Reviewer Comment

- *Labeling will describe the Year 1 PI and use the Kaplan-Meier method for the cumulative 5-year pregnancy rate. The Kaplan-Meier method is a more appropriate statistic for cumulative rates.*

6.1.2 Demographics

The LCS16 Efficacy Study
The demographics and baseline characteristics of the 1,452 women treated with LCS16 are presented in Table 7 below. The mean age of the subjects was 27 years. Most of the subjects were Caucasian (80.2%) and parous (60%). The subjects in the extension group were similar to subjects in the no-extension group in regard to demographics and baseline characteristics. See Table 7 below.

Table 7 LCS16, Baseline Demographics, LCS16 Efficacy Study

Variable	LCS16 No-extension N = 745 (100%) n (%)	LCS16 Extension N = 707 (100%) n (%)	Total N = 1,452 (100%) n (%)
Ethnic group			
• Caucasian	581 (78.0)	583 (82.5)	1,164 (80.2)
• Black	55 (7.4)	19 (2.7)	74 (5.1)
• Hispanic	81 (10.9)	78 (11.0)	159 (11.0)
• Asian	9 (1.2)	8 (1.1)	17 (1.2)
• Other***	19 (2.6)	19 (2.7)	38 (2.6)
Mean age (range)	26.6 (18-35)	27.6 (18-35)	27.1 (18-35)
• Age ≤ 25 years	310 (41.6)	254 (35.9)	564 (38.8)
• Age > 25 years ≤ 35 years	435 (58.4)	453 (64.1)	888 (61.2)
Mean BMI (kg/m^2) (range)	25.54 (15.2-56.5)	25.09 (15.2-57.6)	25.32 (15.2-57.6)
• **< 30 kg/m^2**	601 (80.7)	597 (84.4)	1198 (82.5)
• **≥ 30 kg/m^2**	142 (19.1)	108 (15.3)	250 (17.2)
Parity			
• Nulliparous	312 (41.9)	262 (37.1)	574 (39.5)
• Parous	433 (58.1)	445 (62.9)	878 (60.5)
Currently sexually active	733 (98.4)	702 (99.3)	1,435 (98.8)
Current smokers	190 (25.5)	170 (24.0)	360 (24.8)
Mean uterine length in mm (range)	72.3 (45-111)	72.7 (45-124)	72.5 (45-124)
# of subjects with history of ectopic pregnancy	1	2	3

N = Total number of LCS16 treated subjects (FAS=1,452)
*Number of LCS16 subjects in the FAS who did not enter into the extension phase.
**Number of LCS16 subjects in the FAS who entered the extension phase.
***American Indian, South American. Pacific Islander, Creole, Egyptian etc.
Source: CSR PH-37274, Page 73, Table 8-7, Page 109, Table 14.1/24, Page 232, Table 14.1/76

Reviewer Comments

- *A total of 98.9% of women gave a history of regular menstrual cycles. Only 1.2% of women in the LCS16 group reported a history of irregular cycles.*
- *At the pre-IND meeting held April 4, 2006, the Division requested data for a minimum of 10,000 28-day equivalent cycles for the first year of use and that a total of 45% of these cycles should be from subjects in North America. This request was successfully met by the Applicant.*

The Phase 2 Study

The phase 2 Study was done entirely in Europe. The mean age of the subjects in the LCS16 group was 32 years (overall range at screening 21 to 41 years). About 20% of the women had never given birth before. Almost all women (99%) were Caucasian/white. Baseline demographics are listed in Table 8 below.

Table 8 LCS16, Baseline Demographics, Phase 2 Study

Variable	LCS16 N=245 (100%) n (%)
Ethnic group	
• Caucasian	244 (99.6)
• Asian	1 (0.4)
Mean age in years (range)	32.1 (21-41)
• 18 to 25 years	34 (13.9)
• 26 to 35 years	134 (54.7)
• > 35 years	77 (31.4)
• 18 to 35 years (efficacy population)	168 (68.6)
Mean BMI (kg/m^2) (range)	26.7 (16.4-43.5)
• < 30 kg/m^2	219 (89.4)
• ≥ 30 kg/m^2	26 (10.6)
Parity	
• Nulliparous	49 (20.0)
• Parous	196 (80.0)

Source: Summary of Clinical Efficacy, Page 31, Table 3-10

Reviewer Comments

- *Women in the LCS16 Efficacy study were younger (mean age of 27) than the women in the phase 2 study (mean age of 32). This was probably due to the different inclusion criteria (18 to 35 years in the LCS16 Efficacy study vs. 21 to 40 years in the phase 2 study).*
- *The proportion of nulliparous women was also noticeably higher in the phase 3 study (39.5% vs. 20.0%).*
- *No other clinically relevant differences were observed for the other demographic parameters.*

6.1.3 Subject Disposition

The LCS16 Efficacy Study

Women were recruited from 138 centers and 11 countries for this study. A total of 109 sites continued into the extension phase.

A total of 3,661 women were screened for the study and a total of 2,885 women were randomized to treatment. Of the 776 women (21.2%) who were screened but not randomized, 401 did not meet the inclusion and exclusion criteria, 164 withdrew consent, 85 had no further information available, 44 could not be included due to pregnancy, and 82 discontinued for other reasons.

From the LCS12 and LCS16 arm, 819 (57%) and 870 subjects (60%), respectively, completed the 3-year study.

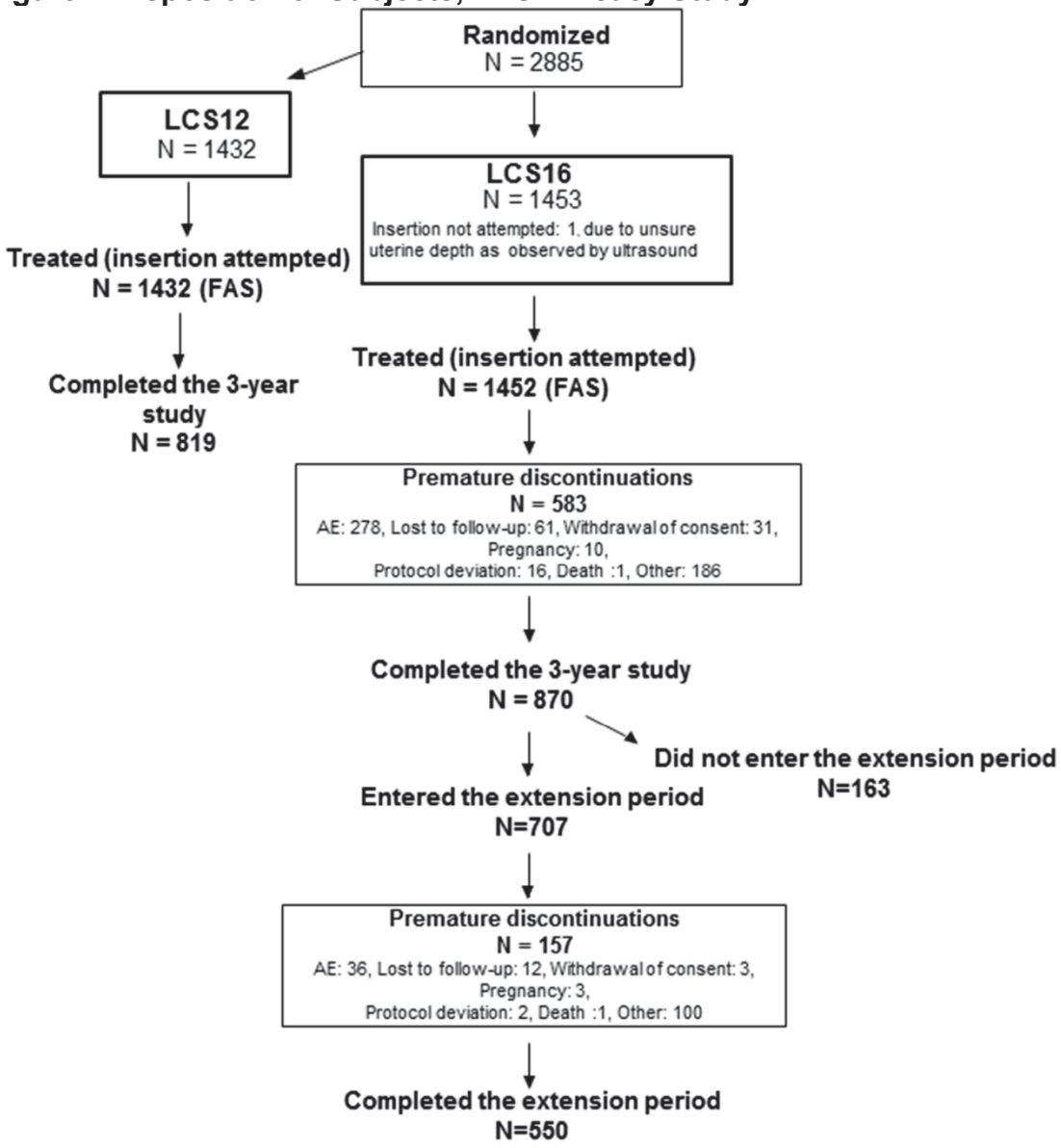
Reviewer Comment

- *LNG IUS insertion was not attempted in 1 subject (Subject 245532) in the LCS16 group because the ultrasound examination could not adequately define the uterine depth.*

LCS16 Efficacy Study-Extension Period

Of the 870 subjects that completed the 3-year treatment in the LCS16 treatment group, 707 subjects (81%) continued in the LCS16 extension phase. A total of 157 subjects (22%) discontinued LCS16 use prematurely during the extension period and 550 subjects (78%) completed the extension study (see Figure 2).

Figure 2 Disposition of Subjects, LCS Efficacy Study



Source: CSR PH-37274, Page 66, Figure 8.1

Discontinuations

Table 9 below gives an overview of the number of subjects who prematurely discontinued LCS16 treatment after randomization during the first 3 years of the study and during the extension phase of the study.

During the first 3 years, 583 subjects (40.1%) discontinued LCS16 treatment prematurely and the most common reason for discontinuation was AE for 278 subjects (19.1% of the randomized subjects).

In the extension phase, 157 subjects (22.2%) discontinued the study prematurely. A total of 36 (5.1%) discontinued due to AEs.

Table 9 LCS16, Subject Dispositions, LCS16 Efficacy Study

Parameter	Randomized (N = 2885)	
	LCS16 First 3 Years N=1453 n (%)	LCS16 Extension (After Year 3) N=707 n (%)
Study medication administered	1452[1] (>99)	707 (100.0)
Completed study phase	163 (11.2)[2]	550 (77.8)
Premature discontinuations	583 (40.1)	157 (22.2)
Reason for discontinuation		
• Adverse event	278 (19.1)	36 (5.1)
• Lost to follow-up	61 (4.2)	12 (1.7)
• Withdrawal of consent	31 (2.1)	3 (0.4)
• Protocol deviation	16 (1.1)	2 (0.3)
• Pregnancy	10 (0.7)	3 (0.4)
• Death	1 (<0.1)	1 (0.1)
• Other[3] o Desired pregnancy	186 (12.8) 117 subjects	100 (14.1) 62 subjects

[1] Insertion not attempted in one subject due to undefined uterine depth on ultrasound. Therefore, this subject was not included in the FAS cohort of 1452 subjects
[2] These 163 subjects completed the 3 year phase but did not enter the extension phase.
[3] Mainly wish for pregnancy but also includes a failed insertion, no further need for contraception, moving away, unable to attend visits, personal reasons
Source: Adapted from CSR PH-37274, Page 67, Figure 8.2

Reviewer Comments

- *As listed above, approximately 40% of the subjects randomized to LCS16 did not complete the full 3-year course of the study and 22% did not complete the extension phase.*
- *Most discontinuations were due to an adverse event.*

Discontinuations by parity are shown in the Table 10 below.

Table 10 LCS16, Discontinuations by Parity, LCS16 Efficacy Study

Parity	Reason for Discontinuation	LCS16 No-exten. N = 746[1] n (%)	LCS16 Extension N=707 n (%)	LCS16 Total N = 1452[2] n (%)
Nulliparous Subjects		312 (100.0)	262 (100.0)	574 (100.0)
	Withdrawal of consent or AE	130 (41.7)	17 (6.5)	147 (25.6)
	Progestin-related side effect[3]	20 (6.4)	1 (0.4)	21 (3.7)
	Bleeding, incl. amenorrhea	32 (10.3)	3 (1.1)	35 (6.1)
Parous Subjects		433 (100.0)	445 (100.0)	878 (100.0)
	Withdrawal of consent or AE	179 (41.3)	22 (4.9)	201 (22.9)
	Progestin-related side effect[3]	20 (4.6)	4 (0.9)	24 (2.7)
	Bleeding, incl. amenorrhea	39 (9.0)	2 (0.4)	41 (4.7)
Total Subjects		745[2] (100.0)	707 (100.0)	1452 (100.0)
	Withdrawal of consent or AE	309 (41.5)	39 (5.5)	348 (24.0)
	Progestin-related side effect[3]	40 (5.4)	5 (0.7)	45 (3.1)
	Bleeding, incl. amenorrhea	71 (9.5)	5 (0.7)	76 (5.2)

[1] For 1 subject (245532), insertion was not attempted due to unsure uterine depth as observed by ultrasound.
[2] FAS population
[3] Breast tension, breast pain, headache, nausea, mood changes, bloating, edema, weight gain, acne or greasy skin,
Source: CSR PH-37274, Page 68, Table 8-3

Reviewer Comments

- *The total number of subjects treated with LCS16 who discontinued due to AE or withdrawal of consent was 348 (24.0%).*
- *No major difference was seen between nulliparous and parous subjects (25.6% vs. 22.9%).*
- *Significantly fewer subjects in the extension group discontinued the study due to progestin-related side effects and bleeding/amenorrhea.*

Drug Exposure

Cumulative drug exposure for all LCS16 treated women is listed in Table 11.

Table 11 LCS16, Drug Exposure, (WY), LCS16 Efficacy Study

Duration of Exposure	Subjects treated for at least this duration	Total LCS16 Exposure (WY*)	LCS16 Evaluable Exposure**
Year 1	**1,452**	**1,316.41**	**1,252.43**
Year 2	1,206	1,105.32	1,066.87
Year 3	1,010	926.28	897.75
Year 4	773	677.18	659.17
Year 5	636	581.53	558.30
2 years cumulative	1,452	2,421.73	2,319.30
3 years cumulative	1,452	3,348.01	3,217.05
4 years cumulative	1,452	4,025.18	3,876.22
5 years cumulative	**1,452**	**4,606.71**	**4,434.53**
Total	1,452	4,611.99	4,437.31

* A woman-year = 365 days
**Total exposure minus the time (in months) in which backup contraception was used or sex hormones were taken for other reasons.
Source: CSR PH-37274, Page 83, Table 9.1

Reviewer Comment

- *The mean treatment duration (including the extension period) for all LCS16-treated women was 1,160 days or 3.18 WY.*
- The evaluable exposure in the 5-year study was 4,434.53 woman years (WY) or 57,649 28-day cycle equivalents.

6.1.4 Analysis of Primary Endpoint(s)

6.1.4.1 LCS16 Efficacy Study

The primary pregnancy rate for LCS16 was based on data from women 18 to 35 years of age during the first year of use (Year 1 PI) and for the total treatment duration of 5 years (5-year PI). The primary efficacy population included all women in the FAS, which was defined as all randomized women who received LCS16 treatment (successful or unsuccessful insertion) (N=1452).

Contraceptive efficacy was assessed by calculating the PI and performing a Kaplan-Meier life-table analysis based on the number of pregnancies occurring during study treatment or for which the estimated date of conception was within 7 days after the LCS16 removal or detection of expulsion. Months in which conception did not occur but which included the use of back-up contraception or exclusionary concomitant sex steroids were not included in the calculation of the PI.

A total of 1,452 subjects were treated (i.e., had at least one insertion attempt) with LCS16. From these, 1,445 subjects (99.5%) had a successful insertion. Of the 1,445 successful insertions, a total of 1,390 were successful at the first attempt and 55 were

successful at the second attempt. In 7 subjects (0.5%), the LCS16 was not successfully inserted.

Treatment compliance was documented by checking the visibility of the IUS threads and by confirming the location of the LCS16 by vaginal ultrasound at all visits after insertion. Treatment compliance was defined as the LCS16 being correctly positioned in the uterine cavity ('*in situ*') or displaced within the uterine cavity (displaced, intrauterine) but still completely within the cavity. Subjects were non-compliant if the IUS was displaced in the cervical canal, expelled into the vagina, had perforated the cervix, the myometrium or the peritoneum, or was absent

A total of 13 pregnancies occurred in subjects using LCS16 during the entire 5-year study. A total of 10 occurred during the 3-year study and an additional 3 pregnancies occurred during the 2-year extension period.

There were no pregnancies documented with an estimated date of conception before the start of the study treatment or within the 7-day window post IUS removal or expulsion.

Reviewer Comment

- *All women were contacted by the study sites after the end of the study to determine if they had become pregnant within 3 months after the end of the study treatment or discontinuation.*

The evaluable exposure in the 5-year study was 4,434.53 woman years (WY) or 57,649 28-day cycle equivalents. As expected due to decreasing subject numbers, the highest evaluable exposure by single year was seen during the first year, with 1,252 woman years of exposure followed by the second year (1,067 WY), third year (898 WY), fourth year (659 WY) and fifth year (558 WY).

A total of 13 pregnancies were observed on LCS16 treatment. Of these, 8 pregnancies were ectopic. Of the remaining 5 pregnancies, 2 ended in spontaneous abortion, 1 ended in missed abortion and 2 pregnancies were normal and carried to term.

The earliest estimated date of conception was 283 days after insertion (Subject 160423) and the latest estimated date of conception was 1558 days after insertion (Subject 120324).

Table 12 LCS16, Reported Pregnancies, LCS16 Efficacy Study

Patient ID No.	Age, Parity BMI Ethnicity/Country	IUS Insertion-Removal/ Expulsion	Estimated Conception Date	Days Post Insertion	Comment
Years 1 to 3 (10 pregnancies)					
160423	26 years, parous 35 kg/m² Caucasian/Finland	12/18/2007 - 10/9/2008	9/26/2008	283	-Ectopic pregnancy
160927	33 years, parous 19.9 kg/m² Caucasian /Finland	10/22/2007-2/10/2010	12/10/2009	780	-Blighted ovum -Spontaneous abortion
180112	33 years, parous 33.8 kg/m² Caucasian/Hungary	12/4/2009-6/4/2009	5/2/2009	515	-Spontaneous abortion
180317	33 years, parous 31.5 kg/m² Caucasian/Hungary	11/22/2007-1/3/2009	12/7/2008	381	-Ectopic pregnancy
200609	32 years, parous 19.9 kg/m² Caucasian/Netherlands	1/3/2008-12/21/2009	10/?/2009	671	-Ectopic pregnancy regressed spontaneously
242321	31 years, nulliparous 21.1 kg/m² Caucasian/West African/US	4/21/2008-7/9/2010	1/1/2010	620	-Ectopic pregnancy
243228	23 years, parous 27.6 kg/m² Caucasian/US	5/20/2008-5/6/2009	3/28/2009	312	-Ectopic Pregnancy -Right salpingostomy
243703	26 years, parous 42.9 kg/m² African-American/US	12/13/2007-2/10/2010	2/8/2010	788	-Total expulsion -Healthy female born (b) (6)
243932	29 years, nulliparous 21.3 kg/m² Caucasian/US	2/21/2008-3/8/2011	2/1/2011	1076	-Ectopic pregnancy treated with Methotrexate
244519	25 years, nulliparous 26.9 kg/m² Caucasian/US	4/10/2008-6/18/2010	6/8/2010	789	-Ectopic pregnancy
Years 4 and 5 (3 pregnancies)					
120324	32 years, parous 25.2 kg/m² Amer. Indian/Argentina	5/1/2008-9/21/12	8/6/2012	1558	-Partial expulsion -Last in-situ 5/21/12 -Healthy male born (b) (6)
170411	23 years, nulliparous 26.3 kg/m² Caucasian/France	1/3/2008-6/7/2011	5/17/2011	1230	-Ectopic pregnancy -Treated with Methotrexate
180616	33 years, parous 18.7 kg/m² Caucasian/Hungary	11/22/2007-3/9/2012	2/16/2012	1547	-Missed abortion - Treated by vacuum aspiration

Sources: Adapted from Summary of Clinical Efficacy, Page 62-64, Table 3-25 and from Integrated Analysis, Page 370, Table 1.2/25

Reviewer Comment

- *The earliest estimated date of conception was 283 days post insertion (Subject 160423).*

Pregnancies by Year

A total of 2 pregnancies occurred during the first year, 4 during the second year, 4 during the third year, 1 during the fourth year and 2 during the fifth year.

Table 13 LCS16 Pregnancies by Year, FAS, LCS16 Efficacy Study

LCS16 Efficacy Study	LCS16 N=1672 (100%)			
	Term	**Ectopic**	**Abortions**	**Total**
Year 1	0	2	0	2
Year 2	0	3	1	4
Year 3	1	2	1	4
Total 3 Years	**1**	**7**	**2**	**10**
Year 4	0	1	0	1
Year 5	1	0	1	2
Total 5 Years	**2**	**8**	**3**	**13**

Source: Adapted from Summary of Clinical Efficacy, PH-37274, Page 55, Table 3-21

Pearl Index

Table 14 lists the calculated unadjusted PIs by year and treatment. Exposure data is based on the number of days of individual exposure converted to woman-years.

The overall PI was **0.29** 95% CI (0.16; 0.50) and the yearly PIs were equal to or below 0.45. The highest PI (0.45) was seen at Year 3 95% CI (0.12; 1.14) followed by Year 2 with a PI of 0.37 95% CI (0.10; 0.96) and Year 5 with PI of 0.36 95% CI (0.04; 1.29)

Table 14 LCS16 PI by Year, FAS, LCS16 Efficacy Study

Treatment	N	Pregnant	Total Exposure (WY) [1]	Evaluable Exposure (WY)[2]	Pearl Index (95% CI)
Year 1	1452	2	1316.41	1252.43	**0.16 (0.02, 0.58)**
Year 2	1206	4	1105.32	1066.87	0.37 (0.10, 0.96)
Year 3	1010	4	926.28	897.75	0.45 (0.12, 1.14)
Year 4	773	1	677.18	659.17	0.15 (0.00, 0.85)
Year 5	636	2	581.53	558.30	0.36 (0.04, 1.29)
5 years	1452	13	4606.71	4434.53	**0.29 (0.16, 0.50)**

[1]One woman-year = 365 days.
[2]Total exposure minus the time (in months) in which backup contraception was used or sex hormones were taken for other reasons.
Source: CSR PH-37274, Page 83, Table 9.1

Reviewer Comments

- *The FDA statistician replicated the Applicant's calculations.*
- *The 1-Year and cumulative 5-Year PIs, are the primary efficacy endpoints. As shown above, these were acceptable at **0.16** (0.02; 0.58) and **0.29** (0.16; 0.50). PIs for each of the 5 years of the study were equal to or below 0.45.*
- *The unadjusted and adjusted PIs were almost identical, because no pregnancies were excluded for the calculation of the adjusted PIs. There were only a few partial expulsions so the exposure times were almost the same as well.*
- *These data provide no evidence that contraceptive efficacy improves or decreases markedly over time.*

The Division requested that the PI also be calculated based on completed 28-day cycle equivalents. The unadjusted PIs for each year and for the 5 years of treatment for women between 18 and 35 years of age using the 28-day cycle exposure data (i.e., 1 WY equals 13 cycles; time with back-up contraception subtracted in terms of 28-day cycles) are shown below in Table 15.

Table 15 LCS16 PI Based on 28-Day Cycle Equivalents, LCS16 Efficacy Study, FAS

Time	Subjects/ Pregnancies	Evaluable Exposure (WY)*	Evaluable Exposure (28-Day Cycles)	Pearl Index (95% CI)
Year 1	1414 / 2	1246.69	16,207	**0.16 (0.2, 0.58)**
Year 2	1182 / 4	1065.62	13,853	0.38 (0.10, 0.96)
Year 3	990 / 4	893.08	11,610	0.45 (0.12, 1.15)
Year 4	717 / 1	658.15	8,556	0.15 (0, 0.85)
Year 5	623 / 2	545.15	7,087	0.37 (0.04, 1.33)
Cum. 5 Years	1414 / 13	4408.69	57,313	**0.29 (0.16, 0.50)**

*One WY = 13 28-day cycles = 364 days
Source: Integrated Analysis of Safety and Efficacy, Page 373, Table 1.2/26

Reviewer Comments

- *The FDA statistician replicated the Applicant's calculations.*
- *The PI analysis based on 28-day cycles did not reveal any significant differences compared to the PI analysis based on the exposure in woman-years.*

The cumulative 5-Year Pearl Indices stratified by age, parity and BMI are shown below in Table 16.

Table 16 LCS16 Cumulative 5-Year PIs by Subgroup, LCS16 Efficacy Study, FAS

	LCS16		
	Women/ Pregnancies	**Evaluable Exposure Time Women/Years[1]**	**Pearl Index (95% CI)**
Cumulative 5-Year PIs by Age			
Total (18-35 years)	1452 / 13	4434.53	0.29 (0.16; 0.50)
-18-25 years	564 / 3	1628.76	0.18 (0.04; 0.54)
-26-35 years	888 / 10	2806.55	0.36 (0.17; 0.66)
Cumulative 5-Year PIs by Parity			
-Nulliparous	574 / 4	1636.80	0.24 (0.07; 0.63)
-Parous	878 / 9	2800.51	0.32 (0.15; 0.61)
Cumulative 5-Year PIs by BMI			
< 30kg/m^2	1198 / 9	3703.97	0.24 (0.11; 0.46)
≥ 30kg/m^2	250 / 4	721.27	0.55 (0.15; 1.42)
Region			
-US	563 / 5	1446.95	0.35 (0.11; 0.81)
-Non-US	889 / 8	2990.36	0.27 (0.12; 0.53)

[1] 1 WY = 365 days
Source: Clinical Study Report PH-37274, Page 84, Table 9-2 and FDA statistical review.

Reviewer Comments

- *The 5-year PI for younger women ages 18-25 years was lower than in the older age group 26-35 years, but all confidence intervals overlap.*
- *The 5-year PIs for the nulliparous and parous subgroups are similar based on the 95% CIs.*
- *The PI for thinner women was lower than that for the subgroup of heavier women but the small size of the heavier BMI subgroup resulted in wide 95% CIs.*
- *The PIs by parity, age-group and BMI showed results similar to those for the overall population. Due to the small number of pregnancies is it difficult to draw conclusions based on the small numerical differences.*
- *The Division usually subgroups by race/ ethnicity (white/Caucasian, black/African American, Hispanic, Asian, other), but the vast majority (approximately 80%) of study subjects in each IUS dosage group were white/Caucasian. Therefore, it would be difficult to draw meaningful conclusions due to the small size of the other racial groups.*
- *The FDA statistician's cumulative 5-Year PI calculations were consistent with the Applicant's calculations.*

The cumulative 5-year failure rate for pregnancy, calculated using the Kaplan-Meier method, for the entire population and by age group, parity and BMI is presented in Table 17. The cumulative failure rate over 5 years was 1.4% (95% CI 0.82; 2.53), which is in line with the cumulative failure rate over 3 years (1.0%) reported for subjects on LCS16 in the 3-year report.

Table 17 LCS16 Cumulative Failure Rate, FAS and by Subgroups (K-M Analysis)

	LCS16 Efficacy Study		
	Women/ Pregnancies	**Relevant Exposure Time Women/Years**	**Cumulative Failure Rate, (95% CI)**
Failure rates by year, FAS (all women 18-35 years)			
Year 1	1452 / 2	1252.43	0.18 (0.04; 0.71)
Year 2	1206 / 4	1066.87	0.37 (0.14; 0.99)
Year 3	1010 / 4	897.75	0.42 (0.16; 1.12)
Year 4	773 / 1	659.17	0.15 (0.02; 1.04)
Year 5	636 / 2	558.30	0.33 0.08; 1.32)
Cum. 5-year	1452 / 13	4434.53	**1.45 (0.82; 2.53)**
Cumulative 5-year failure rate for women by age			
18-25 years	564 / 3	1628.02	0.91 (0.28; 2.93)
26-35 years	888 / 10	2806.51	1.75 (0.93; 3.30)
Cumulative 5-year failure rate for women by parity			
Nulliparous	574 / 4	1636.24	1.23 (0.45; 3.30)
Parous	878 / 9	2798.28	1.55 (0.79; 3.05)
Cumulative 5-year failure rate for women by BMI			
< 30 kg/m^2	1198 / 9	3701.88	1.29 (0.66; 2.53)
≥ 30 kg/m^2	250 / 4	720.57	2.15 (0.81; 5.67)

Source: Clinical Study Report PH-37274, Page 85, Table 9-4

Reviewer Comments

- *The probability of getting pregnant using LCS16 over 5 years in various subgroups is shown above. Similar to the PIs, there were no relevant differences in terms of parity or BMI based on the wide and overlapping CIs.*
- *The PI and Kaplan-Meier calculations based on data derived from the LCS16 efficacy study strongly support the efficacy of LCS16 over the 5 year time period.*

Ovarian Function Substudy (Subset 1)

Ovulation was assessed based on serum progesterone values. Ovulation was defined as a progesterone value of ≥ 2.5 ng/mL. Based on this definition, ovulation occurred as noted below:

- In Year 1: 11/12 (91.7%) women showed evidence of ovulation
- In Year 2: 9/10 (90%) women showed evidence of ovulation

- In Year 3: 7/7 (100%) women showed evidence of ovulation
- In Year 4: 1/1 (100%) women showed evidence of ovulation
- In Year 5 : No subjects were studied

Reviewer Comments

- *Most of the subjects in this small substudy showed evidence of ovulation.*
- *The substudy provides evidence that ovulation suppression is not the primary mechanism of action of the lower dose IUSs.*

6.1.4.2 The Phase 2 Study

A total of 742 women were randomized to treatment in the phase 2 study. Only randomized women with a successful IUS insertion were included in the FAS. Subjects who had an unsuccessful insertion were not included.

Of the 742 women:

- 738 (99.5%) had an LNG-IUS successfully placed.
  - LCS12: 239/240 had successful insertions
  - LCS16: 245/246 had successful insertions
  - Mirena: 254/256 had successful insertions

The mean treatment duration was:

- 915 days or 2.51 WY in the LCS12 group
- 912 days or 2.50 WY in the LCS16 group
- 895 days or 2.45 WY in the Mirena group

Reviewer Comments

- *Evidence for the efficacy of LCS16 was based on the phase 3 LCS16 Efficacy study only. The phase 2 study was submitted as supportive data. This study was primarily a dose-finding study and was not adequately powered to determine precise PIs for each dose.*
- *More importantly, the formulation used in the LCS16 IUS in this study contained 19 mg LNG. The LCS16 formulation used in the LCS16 Efficacy study contained 19.5 mg LNG, which is the to-be marketed formulation. It is difficult to determine the effect on efficacy, if any, of the lower LNG dose.*

A total of 7 pregnancies occurred in the LCS16 group (see Table 18). Two (29%) of these 7 pregnancies were ectopic and 2 (29%) ended in a spontaneous abortion. Three subjects delivered at term. One pregnancy in this group occurred in a patient who had an unnoticed expulsion of the IUS. This pregnancy was normal and carried to term.

Reviewer Comments

- *The comparators used in the phase 2 study were LCS12 and Mirena. There were 2 pregnancies in the LCS12 arm and no pregnancies in the Mirena arm, which consisted of only 254 subjects. This review will concentrate mainly on the LCS16 arm of the study.*
- *Inclusion criteria for this study included women ages 21 to 40. One LCS16 pregnancy occurred in a 37 year old subject who had an ectopic. The PI is usually derived from the 18-35 age groups, so only this cohort will be reviewed for efficacy.*

Table 18 LCS16 Reported Pregnancies, Phase 2 Study

Patient ID No.	Age, Parity BMI Ethnicity/Country	IUS Insertion-Removal	EDC*	Days Post Insertion	Comment
120211	37 years, parous 23.4 kg.m^2 Caucasian/Finland	10/10/2005-10/29/08	9/14/08	1070	-Ectopic pregnancy
120528	28 years, parous 25.3 kg/m^2 Caucasian/Finland	6/21/05-11/20/06	11/4/06	501	-Blighted ovum -Spont. abortion
121511	33 years, parous 23.9 kg/m^2 Caucasian/Finland	9/1/05-3/14/07	2/1/07	518	-Spontaneous abortion
160402	27 years, parous 27.6 kg/m^2 Caucasian/UK	10/26/05-4/26/06	4/9/06	165	-Total expulsion, -Healthy baby
161005	26 years, nulliparous 28.3 kg/m^2 Caucasian/UK	9/14/05-8/29/07	7/19/07	673	-Ectopic pregnancy
140618	22 years, nulliparous 34.2 kg/m^2 Caucasian/Norway	7/8/05-6/20/08	6/22/08	1080	-Conceived 2 days after IUS removal -Delivered (b) (6)
150415	30 years, parous 27.5 kg/m^2 Caucasian/Sweden	9/29/05-11/24/06	11/27/06	424	-Discontinued due to wish for pregnancy -Conceived 3 days after IUS removal. Normal delivery at (b) (6)

*Estimated date of conception
Source: Adapted from Summary of Clinical Efficacy, Page 58, Table 3-25

The Year 1 PI for the LCS16 group in women 18-35 years of age in this study, based on a relevant exposure of 158.62 WY, was 0.63. The cumulative 3-year PI for the LCS16 group, based on a relevant exposure of 401.31 WY, was calculated as 1.50 (see Table 19).

Table 19 LCS16 PIs, 18-35 Year Subgroup, Phase 2 Study

	LCS16				LCS12
	# of Women/ #Pregnancies	Evaluable Exposure* (WY)*	Evaluable Exposure* (Cycles)**	Pearl Index (95% CI)	#Women/ #Pregnancies PI (95% CI)
Year 1 PI	168/1	158.62	2062	**0.63** (0.02,3.51)	154/1 0.07 (0.07,3.87)
Year 2 PI	142/4	131.77	1713	**3.04** (0.83,7.77)	138/1 0.83 (0.02,4.62)
Year 3 PI	124/1	110.92	1442	**0.90** (0.02,5.02)	0
Cum. 3-Year PI	168/6	401.31	5217	**1.50** (0.55,3.25)	154/2 0.55 (0.07,1.97)

*Total exposure time excluding the time in which concomitant contraception was used or sex steroids were taken for any reason.
* 1 WY refers to 13 cycles (13 cycles x 28 days/cycle = 364 days)
** Only subjects with at least one completed cycle in the respective time interval are considered
Sources: Adapted from the Summary of Clinical Efficacy, Page 73 of 117, Table 3-29 and the Integrated Analysis, Page 378 of 704, Table 1.2/27

Reviewer Comments

- *The phase 2 study was not adequately powered to determine precise PIs for each LCS dose. The number of women randomized to LCS16 was relatively small, hence the wide CIs.*
- *LCS12 PIs are included for comparison. There were no pregnancies in the Mirena group (N=254).*

Ovarian Function Substudy (Subset 1)

Ovulation was assessed based on serum progesterone and estradiol levels. All subjects with progesterone values of ≥ 2.5 ng/mL and estradiol values of > 27.24 pg/mL were assessed as having an ovulation. Based on this definition, ovulation occurred as noted below:

- In Year 1 : 12/14 (85.7%) women showed evidence of ovulation
- In Year 2 : 10/10 (100%) women showed evidence of ovulation
- In Year 3 : 9/9 (100%) women showed evidence of ovulation

Reviewer Comment

- *Most of the subjects in this small substudy showed evidence of ovulation. The data from this substudy are consistent with the phase 3 efficacy study regarding evidence for ovulation and provides further evidence that ovulation suppression is not the primary mechanism of action of LCS16.*

6.1.5 Analysis of Secondary Endpoints(s)

The data on menstrual bleeding were analyzed for the FAS and are based on the pooled studies. The occurrence of bleeding was recorded daily using diaries supplied by the Applicant. Subjects made daily entries in the diary recording light, normal or heavy bleeding (in relationship to the subject's normal menstruation), no bleeding, or spotting only, and were instructed to bring the diary to all visits.

Reviewer Comment

- *The Applicant used data based on 90-day reference periods over the entire course of treatment as recommended by the WHO. However, the Division prefers that bleeding data also be analyzed in terms of completed 28-day reference periods, as this is more relevant to clinicians.*

Table 20 LCS16, Subjects with at Least One Bleeding/Spotting Day, 28-Day Cycle Equivalent, Pooled Data

28-Day Period N (%)	Subjects with at least one bleeding or spotting day n (%)	Number of bleeding/spotting days Mean (SD) Median
1 1619 (100.0%)	1612 (99.6)	15.9 (7.6) 16.0
2 1619 (100.0%)	1540 (95.1)	12.4 (7.5) 11
3 1600 (100.0%)	1445 (90.3)	9.3 (6.7) 8.0
4 1575 (100.0%)	1386 (88.0)	7.8 (6.0) 7.0
5 1564 (100.0%)	1318 (84.3)	6.7 (5.6) 6.0
6 1544 (100.0%)	1273 (82.4)	6.3 (5.2) 6.0
7 1518 (100.0%)	1236 (81.4)	5.7 (4.9) 5.0
8 1497 (100.0%)	1170 (78.2)	5.1 (4.7) 4.0
9 1481 (100.0%)	1134 (76.6)	5.0 (4.7) 4.0
10 1450 (100.0%)	1120 (77.2)	4.9 (4.5) 4.0
11 1425 (100.0%)	1012 (71.0)	4.5 (4.4) 4.0
12 1416 (100.0%)	1021 (72.1)	4.3 (4.2) 4.0
24 1218 (100.0%)	818 (67.2)	3.5 (3.6) 3.0
36 1034 (100.0%)	680 (65.8)	3.3 (3.5) 3.0
48 647 (100.0%)	398 (61.5)	2.8 (3.2) 2.0
60 554 (100.0%)	338 (61.0)	2.9 (3.1) 2.0

Source: Integrated Statistical Analysis, Page 426-432, Table 1.2/35 and Page 458-459, Table 1.2/39

Reviewer Comments

- *The mean number of subjects with bleeding/spotting and the mean number of days with bleeding/spotting decreased over time.*
- *The first 28-day period includes the menses during which the IUS was inserted so bleeding/spotting may be more common during this cycle than in other cycles.*

Table 21 is a summary of the bleeding patterns based on 90-day reference periods.

Table 21 LCS16 Bleeding by 90-Day Reference Periods, Pooled Data

	90-Day Reference Periods					
	90 Days N=1566 n (%)	**189 Days N=1511 n (%)**	**270 Days N=1447 n (%)**	**Year 1 N=1371 n (%)**	**Year 3 N=975 n (%)**	**Year 5 N=530 n (%)**
Amenorrhea[1]	3 (0.2)	80 (5.3)	126 (8.7)	168 (12.3)	194 (19.9)	120 (22.6)
Infrequent bleeding[2]	150 (9.6)	307 (20.3)	373 (25.8)	360 (26.3)	250 (25.6)	140 (26.4)
Frequent bleeding[3]	391 (25.0)	147 (9.7)	86 (5.9)	58 (4.2)	23 (2.4)	12 (2.3)
Prolonged bleeding[4]	887 (56.6)	207 (13.7)	99 (6.8)	80 (5.8)	18 (1.8)	6 (1.1)
Irregular bleeding[5]	665 (42.5)	377 (25.0)	248 (17.1)	226 (16.5)	96 (9.8)	50 (9.4)
Normal bleeding[6]	293 (18.7)	573 (37.9)	605 (41.8)	545 (39.8)	410 (42.1)	207 (39.1)

[1]Defined as subjects with no bleeding/spotting throughout the 90-day reference period
[2]Defined as subjects with 1 or 2 bleeding/spotting episodes in the 90-day reference period
[3]Defined as subjects with more than 5 bleeding/spotting episodes in the 90-day reference period
[4]Defined as subjects with bleeding/spotting episodes lasting more than 14 days in the 90-day reference period. Subjects with prolonged bleeding may also be included in one of the other categories (excluding amenorrhea)
[5]Defined as subjects with 3 to 5 bleeding/spotting episodes and less than 3 bleeding/spotting-free intervals of 14 or more days
[6] Defined as none of the above
Source: Integrated Statistical Analysis, Pages 666 to 685, Table 1.2.1/1

Reviewer Comments

- *Amenorrhea increases gradually with continued use, whereas prolonged bleeding decreases. Perhaps women with early amenorrhea are more likely to stay in the study, as opposed to women who have early prolonged bleeding.*
- *Approximately 40% of the subjects who completed the study documented no menstrual irregularities.*

6.1.6 Other Endpoints

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

Reviewer Comment

- *See the Clinical Pharmacology review regarding the pharmacokinetic data.*

6.1.7 Subpopulations

Subpopulations such as nulliparity, age, and BMI are discussed in the relevant sections of the review.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The Applicant is currently seeking approval of only one dose of LNG for the IUS. A higher LNG dose (Mirena) has been approved for 5 years of use and a lower LNG dose (Skyla) has been approved for 3 years of use.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Persistence of efficacy after use and/or tolerance effects was not discussed in the submission. Fertility is expected to return rapidly after the removal of LCS16.

6.1.10 Additional Efficacy Issues/Analyses

No additional efficacy issues/analyses were presented.

7 Review of Safety

Safety Summary

The LCS16 safety database consists of the primary LCS16 Efficacy study (performed in Europe, North America and South America) and the phase 2 study (performed in Europe). The safety cohort of the pooled database consisted of all women who were enrolled and had an insertion attempt, whether successful or not. A total of 1,697 women were assigned to LCS16, 1,672 women assigned to LCS12 and 256 women assigned to Mirena. The total number of women in the safety population for both studies was 3,625. In addition, short-term safety relating to insertion using the (b) (4) inserter was evaluated in the supportive studies using that inserter.

The subject population was generally healthy, 18 to 41-year old females requesting contraception and predominately Caucasian (82.6%). Safety was analyzed based on data pooled across the two studies.

The safety profile of LCS16 did not raise any specific safety concerns.

The most common adverse events reported in the pooled LCS16 group (5-year duration of treatment) were ovarian cyst (21.3%), acne (14.1%), and headache (12.3%).

Drug-related AEs (adverse reactions) were defined as AEs for which the association with the study drug was assessed as missing, possibly, probably, or definitely related by the investigator. The most common drug-related adverse reactions for the pooled LCS16 group were ovarian cyst (14.7%), acne (12.0%), pelvic pain (5.5%), dysmenorrhea (5.4%) and headache (4.8%). The AEs most frequently classified as severe were pelvic pain (2.0%), dysmenorrhea (1.8%), headache (1.5%) and abdominal pain (1.4%).

Reviewer's Comment

- *I agree with the Applicant that these adverse events could be drug-related.*

SAEs were reported in 98 (5.8%) women in the LCS16 group in the pooled phase 2 and phase 3 studies. Of these, 35 SAE's (2.1%) were determined to be drug-related by the Applicant. The most frequent drug-related SAEs were, ectopic pregnancy (10 women, 0.6%), pelvic inflammatory disease (6 women, 0.4%), ovarian cysts (4 women, 0.2%), and abdominal pain (4 women, 0.2%).

Reviewer Comment

- *This reviewer would add hypertension (1 subject; [<0.1%]) and depression (2 subjects; [0.2%]) as possibly being drug-related. Adding these 3 subjects to the Applicant's 22 subjects would result in a total of 25 subjects (1.5%) with drug-related serious adverse reactions.*

The most common AEs causing discontinuation of LCS16 pooled studies were vaginal hemorrhage (53; 3.1%), device expulsion (46; 2.7%), pelvic pain (43; 2.5%) and acne (36; 2.1%).

There were no significant safety problems found in the nulliparous subjects. There were also no relevant safety effects observed with regard to laboratory tests, vital signs, bone mineral density, endometrial histology or other safety parameters measured.

In summary, LCS16 was demonstrated to have an acceptable safety profile in women 18-41 years of age for the proposed 5 year duration of use.

7.1 Methods

Subjects with both successful and unsuccessful insertions were included in the safety evaluation for the LCS16 efficacy study.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The evidence for the clinical safety of LCS16 is based on the LCS16 efficacy study performed in Europe, North and South America) between 2007 and 2013 and the phase 2 clinical study performed in Europe and conducted between 2005 and 2011. The safety data from these studies are presented as a pooled analysis. As discussed earlier

in this review, there were some differences between these two studies in population and size.

- The women in the LCS16 efficacy study (inclusion age 18 to 35 years) were slightly younger than those in the phase 2 study (inclusion age 21 to 40 years). The actual age range of subjects was 18-35 in the LCS16 efficacy study and 20 to 41 in the phase 2 study.
- Subjects in the LCS16 efficacy study came from a broader geographic population (Europe, US, Canada, South America) than those in the phase 2 study (Europe only).
- The LCS16 efficacy study had a much larger population (2,884 women) than the phase 2 study (741 women). In the pooled LCS16 group, 85.6% of the women (1452/1697) were from the LCS16 Efficacy study. Therefore, the results of the pooled analysis are driven by this study.
- The LCS16 Efficacy study had a higher proportion of nulliparous women than the phase 2 study (39.2% vs. 21.6%).
- In the phase 2 study, specific side effects classified as progestin-related (acne, bloating, breast pain, breast tension, edema, headache, mood changes, nausea and weight gain) were assessed at every visit via specific questioning. In contrast, these events were reported voluntarily by women in the LCS16 Efficacy study.

7.1.2 Categorization of Adverse Events

All serious adverse events and common adverse events were reported using Medical Dictionary for Regulatory Activities (MedDRA) Version 17.1.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

In the LCS16 Efficacy study, 2,884 women were assigned to the FAS for the assessment of safety, a total of 1,452 in the LCS16 group and 1,432 in the LCS12 group.

In the phase 2 study, a total of 741 women were assigned to the FAS, among them 245 in the LCS16 group, 240 in the LCS12 group, and 256 in the Mirena group.

Using the pooled data from both studies resulted in 1,697 women assigned to the LCS16 FAS, 1,672 women assigned to the LCS12 FAS, and 256 women assigned to the Mirena FAS (see Table 22).

Table 22 Full Analysis Set, Safety Cohort, Women Ages 18-41

	LCS16	LCS12	Mirena
Phase 3 Study LCS16 Efficacy Study -Study PH-37274 -Protocol 91665/310442	1,452	1,432	0
Phase 2 Study -Study A46796 -Protocol 308901*	245	240	256
Pooled Data	**1,697**	**1,672**	**256**

Source: Summary of Clinical Safety, Page 42, Table 1-4

7.2 Adequacy of Safety Assessments

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

The overall extent of exposure in the studies with LCS16 treatment, the LCS16 Efficacy Study PH-37274 and the Phase 2 Study A46796, is summarized below.

LCS Efficacy Study (Study Report PH-37274) based on 5-years of data collection for LCS16:

- LCS16 (N=1,452): (LCS16 subjects had the option for an extension to 5 years of treatment.)
  - Mean treatment duration = 1,160 days or 3.18 woman-years (WY).
  - Overall exposure = 4,614 WY.
- LCS12 (N=1,432) based on 3-years of data collection:
  - Mean treatment duration = 821 days or 2.25 WY.
  - Overall exposure = 3,219 WY.

Phase 2 Study (Study A46796), which is based on 3-years of data collection:

- LCS16 (N=245):
  - Mean treatment duration = 912 days or 2.50 WY.
  - Overall exposure = 612 WY.
- LCS12 (N=240):
  - Mean treatment duration = 915 days or 2.51 WY.
  - Overall exposure = 602 WY.
- Mirena (N=256):
  - Mean treatment duration = 895 days or 2.45 WY.
  - Overall exposure = 628 WY.

Pooled Studies (PH-37274 and A46796):

- LCS16 (N=1,697):
  - Mean treatment duration = 1,124 days or 3.08 WY.
  - Overall cumulative exposure during the 5-year study = was 5,226 WY or 67,938 28-day equivalent cycles.
- LCS12 (N=1,672):
  - Mean treatment duration = 834 days or 2.29 WY.
  - Overall cumulative exposure during the 3-year study = 3,821 WY.
- Mirena (N=256):
  - Mean treatment duration = 895 days or 2.45 WY.
  - Overall exposure = 628 WY.

Reviewer Comment

- *The differences in the mean treatment duration reflect the differences in the length of the study.*

Table 23 puts the treatment durations in tabular form.

Table 23 Treatment Exposure by Study

	Phase 3 LCS16 Efficacy Study PH-37274 N=2884		Phase 2 Study A46796 N=741		
	LCS16 5-Year	**LCS12 3-Year**	**LCS16 3-Year**	**LCS12 3-Year**	**Mirena 3-Year**
Treatment Duration in Days					
N	1,452	1,432	245	240	256
Mean Days	1,159.8	820.5	911.6	915.1	895.3
Total Days	1,683,967.0	1,174,915.0	223,348.0	219,624.0	229,200.0
Treatment Duration in WY					
N	1,452	1,432	245	240	256
Mean (WY)[1]	3.18	2.25	2.50	2.51	2.45
Total (WY) [1]	4,613.6	3,218.95	611.91	601.71	627.95

[1]A woman year equals 365 days
Source: Summary of Clinical Safety, Page 43, Table 1-5

The pooled overall exposure to LCS16 by year was 1,530 WY (or 19,885 28-day cycles) for the first year, 2,821 WY after 2 years and 3,919 WY at the end of 3 years. At the end of the 5-year extension phase of the LCS16 efficacy study, the cumulative exposure was 5,226 WY (or 67,931 28-day equivalent cycles).

Table 24 below summarizes the pooled treatment exposure by years of use for each IUS.

Table 24 Treatment Exposure, WY, Pooled Data

	LCS16 (Incl. Extension) Pooled Data N=1,697	LCS12 Pooled Data N=1,672	Mirena 3-Year N=256
Year 1	1,530.42	1,487.90	236.30
2 years Cumulative	2,821.04	2,728.48	435.15
3 Years Cumulative	3,918.52	3,778.55	619.18
4 Years Cumulative	4,603.57		
5 Years Cumulative	5,189.35		
Overall Cumulative	5,225.52	3,820.65	627.95

Source: Summary of Clinical Safety, Page 47, Table 1-8

Reviewer Comments

- *Based on the pooled data, a total of 1,206 subjects completed 1 year of LCS16 use and 1,044 subjects completed 3 years of LCS16 use. A total of 707 subjects entered the 2-year extension study and 550 subjects completed the full 5-year LCS16 study.*
- *The pooled safety data of nearly 68,000 cycles of LCS16 exposure over the 5-years of use more than satisfies the Division's safety requirements of 10,000 cycles.*

North American Women
The FAS included 1,287 North American women, of whom 655 received LCS16 and 632 received LCS12.

For the LCS16 North American women:

- 1st treatment year: Total exposure = 7,380 cycles or 568 WY (1 WY equals 13 cycles).
- 3-Year cumulative: Total exposure = 18,158 cycles or 1,396 WY
- 5-Year cumulative: Total exposure = 23,881 cycles or 1837 WY

7.2.2 Explorations for Dose Response

Two doses of LNG (LCS16 and LCS12) were studied in both the phase 2 and phase 3 clinical trials. LCS12 has previously been approved as Skyla, a 3-year intrauterine contraceptive. Approval is currently being sought only for the higher of the two doses (LCS12) as a 5-year intrauterine contraceptive.

7.2.3 Special Animal and/or In Vitro Testing

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

7.2.4 Routine Clinical Testing

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

7.2.5 Metabolic, Clearance, and Interaction Workup

Not applicable for this submission.

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

Routine evaluations for adverse events possibly related to progestin IUSs were performed.

7.3 Major Safety Results

7.3.1 Deaths

Two deaths occurred in the phase 3 LCS Efficacy study. One death was a suicide in a 20 year-old woman (Subject 210112) related to problems with depression and an eating disorder. Her death was assessed by the investigator as unrelated to study drug. The other death occurred in a 33 year old woman (Subject 180709) who was hit by a motorcycle while riding a bicycle and sustained major trauma. Her death was also assessed by the investigator as unrelated to study drug.

There were no deaths during the phase 2 study.

Reviewer Comments

- *Subject 210112 was a 20 year old Caucasian woman who did not report any depression or similar disorders prior to enrollment or during the study. A LCS16 was inserted on* (b) (6)*. The subject's sister died in a plane crash in* (b) (6) *after the IUS insertion. The subject committed suicide in* (b) (6)*. The reasons for her suicide were unknown. The woman's friends reported that she had depression and eating disturbances. Due to the subject's suicide, the LCS16 was never removed.*

  The systemic LNG concentrations with LCS16 are low. The mechanism of action is mainly local. LCS16 does not inhibit ovulation in most women. Because the subject had other co-morbidities contributing to depression and suicide, I agree with the Applicant and the investigator that the suicide was unrelated to the LCS16.

- *Subject 180709 was a 33 year old multiparous woman who had an LCS16 inserted on January 5, 2008. She completed the 3-year study entered the extension phase of the study on December 30, 2010. On* (b) (6)*, she was hit by a motorcycle while riding a bicycle. She was brought to the Emergency Room but resuscitation was unsuccessful. I agree with the Applicant's and the investigator's assessment that this death was not related to the LCS16.*

7.3.2 Nonfatal Serious Adverse Events

Serious adverse events (SAEs) in the pooled LCS16 group were reported in 98 (5.8%) women.

The most frequent drug-related SAEs (or serious adverse reactions [SARs]) in the LCS16 group were ectopic pregnancy (10 women) which included 1 ruptured ectopic pregnancy, pelvic inflammatory disease (6), ovarian cysts (3 women), including a ruptured ovarian cyst and abdominal pain (4).

Drug-Related SARs
The most commonly reported SARs are shown in Table 25 below; note that the LCS16 data are based on the 5-year study period, while data for the two other IUSs were collected over 3 years.

SARs (per the Medical Reviewer) in the LCS16 group were reported in 35 (2.1%) women. These included 10 (0.6%) cases of ectopic pregnancies, 6 (0.4%) cases of pelvic inflammatory disease, 4 (0.2%) cases of abdominal pain, 4 (0.2%) cases of spontaneous abortions, 4 (0.2%) women with ovarian cysts, and 3 (0.2%) women with uterine perforations.

Table 25 Most Frequent SARs* by Preferred Term, Pooled Data

	LCS16 5-Year N=1,697 (100%) n (%)	LCS12 3-Year N=1,672 (100%) n (%)	Mirena 3-Year N=256 (100%) n (%)
Women with any SAE	**98 (5.8)**	**78 (4.7)**	**16 (6.3)**
Women with any SAR	**35 (2.1)**	**10 (0.6)**	**5 (2.0)**
Unruptured/ ruptured Ectopic pregnancy	10 (0.6)	4 (0.2)	0
Pelvic Inflammatory Disease	6 (0.4)	2 (0.1)	1 (0.4)
Abdominal pain	4 (0.2)	4 (0.2)	1 (0.4)
Abortion spontaneous	4 (0.2)[a]	3 (0.2)	0 (0.0)
Depression	3 (0.2)	2 (0.1)	0 (0.0)
Ovarian cyst[b]	4 (0.2)	4 (0.2)	5 (2.0)
Procedural pain	2 (0.1)	0 (0.0)	0 (0.0)
Uterine perforation	2 (0.1)	0 (0.0)	0 (0.0)
Hypertension	1 (<0.1)	1 (<0.1)	0 (0.0)

*In the opinion of the Medical Reviewer
Note: A woman may have had more than one SAE (may appear more than once in this table).
[a] Includes (1) one blighted ovum, (1) one abortion, spontaneous incomplete, (1) one spontaneous abortion, and (1) one missed abortion
[b] Includes a ruptured ovarian cyst, a hemorrhagic ovarian cyst and an ovarian cyst torsion.
Sorted by descending frequency in the pooled LCS16 arm; MedDRA version 17.0
Source: Adapted from Summary of Clinical Safety, Page 96, Table 2-12

Reviewer Comments

- *The pattern of SARs was comparable between the LCS16 Efficacy study and the phase 2 study.*
- *The SAR profile was similar between the LCS16 and LCS12 groups at the end of the 3 year study; however, the majority of drug-related serious ectopic pregnancies and serious pelvic inflammatory disease cases were in the LCS16 group during this period.*

7.3.3 Dropouts and/or Discontinuations

Pooled Data
A total of 375 women (22.1%) in the LCS16 group (over 5 years). and 361 women (21.6%) in the LCS12 group (over 3 years) discontinued the study due to AEs.

There were a total of 46 (2.7%) device expulsions in the LCS16 group and 45 (2.7%) device expulsions in the LCS12 group.

The number of women who discontinued study drug due to an AE or SAE is shown below in Table 26 for the pooled data.

Table 26 Adverse Events Causing Discontinuation by Study Drug, Pooled Data

AE causing study drug discontinuation	LCS16 5-Year N=1,697 (100%) n (%)	LCS16 3-Year N=1,697 (100%) n (%)	LCS12 3-Year N=1,672 (100%) n (%)
Any Adverse Event	**375 (22.1)**	**337 (19.9)**	**361 (21.6)**
Vaginal hemorrhage	53 (3.1)	50 (2.9)	55 (3.3)
Device expulsions	46 (2.7)*	46 (2.7)*	45 (2.7)*
Pelvic pain	43 (2.5)	33 (1.9)	29 (1.7)
Acne	36 (2.1)	33 (1.9)	45 (2.7)
Weight increased	21 (1.2)	21 (1.2)	11 (0.7)
Abdominal pain	17 (1.0)	16 (0.9)	23 (1.4)
Dysmenorrhea	14 (0.8)	13 (0.8)	21 (1.3)
Abdominal pain lower	12 (0.7)	12 (0.7)	19 (1.1)
Dyspareunia	10 (0.6)	9 (0.5)	9 (0.5)
Libido decreased	10 (0.6)	10 (0.6)	8 (0.5)
Ovarian cyst	10 (0.6)	7 (0.4)	4 (0.2)
Mood altered	9 (0.5)	9 (0.5)	8 (0.5)
Uterine spasm	8 (0.5)	8 (0.5)	11 (0.7)
Pelvic inflammatory disease	8 (0.5)	1 (0.4)	5 (0.3)
Ectopic pregnancy	8 (0.5)	1 (0.4)	3 (0.2)
Headache	7 (0.4)	8 (0.5)	8 (0.5)
Abdominal distension	4 (0.2)	4 (0.2)	8 (0.5)
Depression	3 (0.2)	3 (0.2)	9 (0.5)
Uterine hemorrhage	3 (0.2)	3 (0.2)	8 (0.5)

A woman may have had more than one AE
*Not all expulsions were reported as an AE, preferred term device expulsion.
Source: Summary of Clinical Safety, Page 105, Table 2-14

Reviewer Comment

- *Overall, the pattern of AEs that led to study drug discontinuation was comparable between the studies and between the LCS treatment groups.*

7.3.4 Significant Adverse Events

7.3.4.1 Pregnancy, Puerperium and Perinatal Conditions

Using the MedDRA system organ class (SOC) relating to pregnancy complications, Table 27 below lists the most frequent complications in the LCS16, LCS12 and Mirena cohorts. The most frequently occurring complication within this SOC was ectopic pregnancy.

Table 27 Women with Pregnancy-Related Complications, Pooled Data

	LCS16 5-Year N=1,697 (100%) n (%)	LCS12 3-Year N=1,672 (100%) n (%)
Any Pregnancy-Related Complication	**17 (0.9)**	**8 (0.5)**
Unruptured or ruptured ectopic pregnancy	10 (0.6)	4 (0.2)
Pregnancy*	3 (0.2)	0
Complete spontaneous abortion	1 (<0.1)	3 (0.2)
Abnormal uterine contractions	1 (<0.1)	1 (<0.1)
Incomplete spontaneous abortion	1 (<0.1)	0
Blighted ovum	1 (<0.1)	0
Missed abortion	1 (<0.1)	0
Premature separation of placenta	0	1 (<0.1)

* Includes 2 women with blighted ovum/spontaneous abortion and 1 normal pregnancy. A normal pregnancy was documented as an AE in the phase 2 study but not in the LCS16 Efficacy study.
Note: A woman may have had more than one pregnancy-related complication.
Source: Summary of Clinical Safety, Page 127, Table 2-28

In the pooled studies, serious AEs in the SOC were reported for a total of 22 women (0.6%): 15 women in the LCS16 group (0.9%); 7 women in the LCS12 group (0.4%); and no women in the Mirena group.

A total of 4 women in this treatment group had AEs that were a type of spontaneous abortion. These include one blighted ovum, one spontaneous incomplete abortion, one spontaneous compete abortion and one missed abortion. Other serious AEs events reported as pregnancy, puerperium, and perinatal conditions were single cases.

Reviewer Comments

- *A normal pregnancy was documented as an AE in the phase 2 study, but not necessarily in the LCS16 efficacy study. Therefore, the total number of pregnancies in the AE table above (N=25) differs from the actual number of pregnancies (N=29) reported during the studies.*
- *No pregnancies occurred in either study prior to the initiation of study medication.*
- *With the exception of ectopic pregnancy, the frequency of any event was very low in all treatment groups.*

Ectopic Pregnancy

Of the 18 pregnancies in the pooled LCS16 group, a total of 8 women had intrauterine pregnancies (44%) and 10 women (56%) had ectopic pregnancies.

In the LCS16 efficacy study, there were a total of 8 ectopic pregnancies in the LCS16 group, one of which ruptured. In the phase 2 study, there were 2 ectopic pregnancies in the LCS16 group, neither of which ruptured.

All the ectopic pregnancies in both studies were classified as SAEs.

Reviewer Comments

- *If a pregnancy occurs with an IUS in place (compared to pregnancy in a woman not using an IUS), it is more likely to be an ectopic pregnancy, as documented by the percentages above.*
- *The 55% rate of ectopic pregnancy (as a percent of all pregnancies) demonstrated in the LCS16 group is not surprising for an IUS. The Mirena label states that up to half of pregnancies that occur with Mirena in place are ectopic.*
- *Historical prospective data from randomized controlled trials describe a low absolute risk of ectopic pregnancy. This is also reflected in the data for LCS16 from the two clinical trials submitted to this NDA, which demonstrate a Pearl Index of 0.2 for ectopic pregnancy over 5 years of use (see* Table 30*). Per the Mirena label, the incidence of ectopic pregnancy in clinical trials, which excluded women with* (b) (4) *ectopic pregnancy, was approximately 0.1% per year.*

Information on the individual LCS16 subjects with ectopic pregnancies is shown in Table 28 below.

Table 28 LCS16, Ectopic Pregnancies, Pooled Data (N=10)

Subject# / Age Race / Parity	Study onset day	AE duration (days)	Study drug action	Outcome
LCS16 Efficacy Study (N=8)				
160423 / 26 Caucasian/Parous	Day 297	51 days	Drug withdrawn	Recovered, resolved
170411 / 23 Caucasian/Nulliparous	1252 since insertion	79 days	Drug withdrawn	Recovered, resolved
180317 / 33 Caucasian/Parous	Day 409	3 days	Drug withdrawn	Recovered, resolved
200609 / 32 Caucasian/Parous	Day 699	21 days	Drug withdrawn	Recovered, resolved
242321 / 31 Other/Nulliparous	Day 803	1 day (ruptured)*	Drug withdrawn	Recovered, resolved
243228 / 23 Caucasian/Parous	Day 345	2 days	Drug withdrawn	Recovered, resolved
243932 / 29 Caucasian/Nulliparous	Day 1119	80 days	Drug withdrawn	Recovered, resolved
244519 / 25 Caucasian/Nulliparous	Day 799	4 days	Drug withdrawn	Recovered, resolved
Phase 2 Study (N=2)				
120211 / 37 Caucasian/Parous	Day 1100	17 days	Dose not changed**	Recovered, resolved
161005 / 26 Caucasian/Nulliparous	Day 710	10 days	Drug withdrawn	Recovered, resolved

* LCS16 Efficacy Study, subject no. 242321) had a ruptured ectopic pregnancy at year 3, severe in intensity.
**Phase 2 Study subject (no. 120211) was on study drug for more than 3 years and the IUS was already planned to be removed prior to the diagnosis of the ectopic pregnancy AE. The woman had an oophorectomy the same day the ectopic pregnancy was diagnosed, and the IUS removed, as previously planned, 16 days later.
Source: Summary of Clinical Safety, Page 116, Table 2-21.

Reviewer Comment

- *A total of 10 ectopic pregnancies occurred in the pooled LCS16 group. Five of these subjects were nulliparous and five were parous. Only one of these ectopic pregnancies ruptured.*

Table 29 Percent of Subjects with Ectopic Pregnancy, Pooled Data

	LCS16 5-Year Pooled N=1697 10 Pregnancies n (%)	LCS12 3-Year Pooled N=1672 4 Pregnancies n (%)
Time of Event		
Year 1	2/1,697 (0.1)	2/1,672 (0.1)
Year 2	3/1,425 (0.2)	2/1,381 (0.1)
Year 3	3/1,202 (0.2)	0/1150
Year 4	2/884 (0.2)	-
Year 5	0	-
Total 5-Year	10/1697 (0.6)	4/1672 (0.2)
Parity		
Nulliparous	5/623 (0.8)	2/608 (0.3)
Parous	5/1074 (0.2)	2/1064 (0.2)
Age		
18-25 years	3/598 (0.5)	2/604 (0.3)
26 to 35 years	6/1022 (0.5)	2/982 (0.2)
> 35 years	1/77 (1.3)	0/86
BMI		
≤ 30 kg/m^2	8/1417 (0.6)	4/1409 (0.3)
> 30 kg/m^2	2/276 (0.7)	0/262

Source: Adapted from Summary of Clinical Safety, Page 117 Table 2-22

The overall incidence of ectopic pregnancy using the pooled data for LCS16 and LCS12 are shown in Table 30 below. There were no pregnancies in the Mirena arm of the phase 2 study.

Table 30 Ectopic Pregnancy Rates (PI) per Study, Pooled Data

	LCS16 5-Year N=1,697		LCS12 3-Year N=1,672	
	# Ectopic Pregnancies	Pearl Index*	# Ectopic Pregnancies	Pearl Index*
LCS16 Efficacy Study	8	0.18	3	0.10
Phase 2 Study	2	0.33	1	0.17
Pooled	**10**	**0.20 (0.10; 0.36)**	**4**	**0.11 (0.03; 0.28)**

*PI = Pearl Index = ectopic pregnancies occurring per 100 woman-years
Source: Summary of Clinical Safety, Page 114, Table 2-19

Reviewer Comment

- *Ectopic pregnancy rates for both LCS16 and LCS12 are very low. The significance of the higher PI with LCS16 is uncertain but not particularly worrisome.*

Table 31 below presents the ectopic pregnancy rates by duration of treatment.

Table 31 Ectopic Pregnancy Rates per Year, Pooled Data

	LCS16 5-Year Pooled N=1697		LCS12 3-Year Pooled N=1672	
	# Ectopic Pregnancies	**Pearl Index**	**# Ectopic Pregnancies**	**Pearl Index**
1st year	2	0.13 (0.02; 0.49)	2	0.14 (0.02; 0.50)
2nd year	4	0.32 (0.09; 0.81)	2	0.17 (0.02; 0.60)
3rd year	3	0.28 (0.06; 0.82)	0	0.00 (0.00; 0.37)
4th year	1	0.15 (0.00; 0.84)	-	-
5th year	0	0.00 (0.00; 0.66)	-	-
Total	10	**0.20 (0.10; 0.36)**	4	0.11 (0.03; 0.28)

Source: Summary of Clinical Safety, Page 115, Table 2-20 and LCS16 Integrated Analysis, Page 134, Table 1.2/9

Reviewer Comment

- *The ectopic rates for LCS16 are generally evenly spread for the first 4 years. The numbers are small.*

7.3.4.2 Infections

Pelvic inflammatory disease and endometritis are historically associated with IUD use.

Pelvic Inflammatory Disease (PID)

For the assessment of PID, adverse events were identified via the MedDRA Term Grouping (PID, PID mycoplasmal, pelvic infection, salpingitis, salpingo-oophoritis, tubo-ovarian abscess, oophoritis, endometritis, etc.).

The diagnosis of PID was made according to the investigator's clinical assessment. The following diagnostic criteria were provided to guide the investigator in assessing suspected cases of PID.

- Pelvic tenderness on exam
- Lower abdominal pain
- At least 2 of the following:
  - Purulent or abnormal vaginal discharge
  - Increased serum C-reactive protein (S-CRP) > 30 mg/L
  - Increased body temperature (> 38°C)
  - Typical findings of laparoscopy if other clinical evidence is inconclusive
  - Evidence of causative pathogen (*Chlamydia trachomatis* or *Neisseria gonorrhea*) in the cervical canal

Reviewer Comment

- *These were reasonable criteria for the diagnosis of PID.*

A diagnosis of PID necessitated removal of the IUS, and the woman was considered as having discontinued the study treatment. Most of the PID reported was serious, moderate to severe in intensity and was assessed to be related to study drug,

A total of 9 women in the pooled LCS16 group had PID confirmed by the investigator. Six of these 9 confirmed PIDs were classified as SAEs. Eight out of the 9 confirmed PIDs were assessed as related to study drug. All women with diagnosed PID recovered.

In the phase 3 study, a total of 8 women had confirmed PID, 5 of them SAEs, and all 8 related to the study-drug according to the investigator´s assessment.

In the phase 2 study, one SAE relating to PID was reported in the LCS16 arm. This case was reported as severe and required surgery. The investigator believed that a relationship to the study drug was unlikely

Reviewer Comments

- *Subject 120216 was a 37 year old G2P2 (2 prior vaginal deliveries) who had an LCS16 insertion in the phase 2 study on (b) (6) Approximately 61 days after the insertion on (b) (6), she was hospitalized due to severe abdominal pain and fever. She had a laparoscopy and an ovarian abscess was diagnosed. A prophylactic appendectomy was performed and she was placed on antibiotics. By (b) (6), the patient had recovered. The investigator believed that LCS16 causality was unlikely; the Applicant believed that causality was possible.*
- *In this reviewer's opinion, the only reason that causality is unlikely is because of the time course between the insertion of LCS16 and the event. The abscess could have been related to a recent sexually transmitted infection.*

Table 32 Cases of Pelvic Inflammatory Disease, Pooled Data

	LCS16 5-Year Pooled N=1,697	LCS12 3-Year Pooled N=1,672	Mirena N=256
Total no. of women with PID*	9 (0.5%)	6 (0.4%)	1 (0.4%)
Time of event			
• 1st year	6	3	1
• 2nd year	0	1	0
• 3rd year	1	2	0
• 4th year	2	NA	NA
Parity			
• Nullip	2	0	0
• Parous	7	6	1
Age			
• 18-25 years	0	2	0
• 26-35 years	8	4	0
• >35 years	1	0	1
Ethnicity			
• Caucasian	9	6	1
Drug discontinued			
• Yes	8	5	0
• No	1	1	0
• N/A	0	0	1**

*Subject 243319 had 2 consecutive events coded to PID in Year 4, one an AE and one an SAE
** Subject 130222 had the IUS removed prior to the diagnosis of PID
Source: Summary of Clinical Safety, Page 109, Table 2-16

Review Comments

- *The rates of PID with the three IUSs are nearly identical.*
- *Most cases of PID occurred in the first year of treatment and most occurred in parous women.*

Endometritis

For the assessment of endometritis, events were identified via MedDRA preferred term: "endometritis" and included the reported terms: endometritis, endometritis by mycoplasma, suspicion of endometritis, and endometrium inflammation.

A total of 13 women (0.8%) in the LCS16 and 14 women (0.8%) in the LCS12 arm were diagnosed with endometritis. These were not considered as suspicious for PID by the investigators based on clinical presentation. No cases of endometritis were serious; most events were moderate in severity, and occurred most frequently in parous women and during the first year of the study in both the LCS16 Efficacy Study and the phase 2

Study. A total of 4 of the 28 women (14%) with endometritis were withdrawn from LCS16 Efficacy study and the phase 2 study due to this AE.

Table 33 Endometritis Parameters, Pooled Data

	LCS16 5-Year Pooled N=1697	LCS12 3-Year Pooled N=1672	Mirena N=256
Subjects with endometritis	13 (0.8%)	14 (0.8%)	1 (0.4%)
Time of event			
• 1st year	10	11	0
• 2nd year	3	2	1
• 3rd year	0	2	0
• 4th year	2	0	0
Parity			
• Nulliparous	4	3	0
• Parous	9	11	1
Age			
• 18-25 years	3	1	0
• 26-35 years	10	10	1
• > 35 years	0	3	0
Ethnicity			
• Caucasian	13	12	1
• African-American	0	1	0
• Hispanic	0	1	0
Drug Discontinued			
• Yes	2	2	0
• No	11	12	1

Source: Adapted from Summary of Clinical Safety, Page 113, Table 2-18

Reviewer Comments

- *Postpartum endometritis within 3 months prior to the start of the study was an exclusion criterion so as not to confound results.*
- *Endometritis was more frequent in parous women and also more frequent during the first year of study.*
- *The rates of endometritis were less than 1% in all three IUS groups.*

7.3.4.3 Reproductive System and Breast Disorders

The most common reproductive system and breast disorders are listed by preferred term in Table 34. The frequency of these disorders was very low in all treatment groups. The most frequently reported reproductive system and breast disorders were ovarian cyst, cervical dysplasia, pelvic pain and dysmenorrhea.

In the pooled studies, SAEs in this SOC were reported for 7 women (0.3%) in the LCS16 group. Most of these SAEs were ovarian cysts.

Table 34 Frequency of Reproductive and Breast Disorders, Pooled Data

Condition	LCS16 5-Year N=1697 (100%) n (%)	LCS12 3-Year N=1672 (100%) n (%)	Mirena N=256 (100%) n (%)
Any reproductive or breast disorder	**969 (56.6)**	**804 (48.1)**	**144 (56.3)**
Ovarian cyst	362 (21.3)	207 (12.4)	64 (25.0)
Cervical dysplasia	154 (9.1)	112 (6.7)	12 (4.7)
Pelvic pain	136 (8.0)	100 (6.0)	1 (0.4)
Dysmenorrhea	135 (8.0)	144 (8.6)	18 (7.0)
Vaginal hemorrhage	84 (4.9)	76 (4.5)	4 (1.6)
Breast pain	84 (4.9)	56 (3.3)	27 (10.5)
Vaginal discharge	76 (4.5)	69 (4.1)	4 (1.6)
Breast discomfort	60 (3.5)	56 (3.3)	62 (24.2)
Uterine spasm	41 (2.4)	33 (2.0)	1 (0.4)
Breast tenderness	40 (2.4)	33 (2.0)	3 (1.2)
Dyspareunia	36 (2.1)	35 (2.1)	5 (2.0)

A woman may have had more than one reproductive system and/or breast disorder.
Note: Hemorrhagic ovarian cysts (1.2% in the pooled LCS16 group women) and ruptured ovarian cysts (0.5% in the pooled LCS16 group women) are not included in the ovarian cyst counts in this table.
Source: Summary of Clinical Safety, Page 129, Table 2-29

Reviewer Comment

- *Breast pain and breast discomfort were reported more frequently in the phase 2 study because in the phase 2 study, these symptoms classified as progestin-related were specifically assessed at every visit by the investigator. In the phase 2 study, the incidence of breast discomfort and breast pain together was 35% for LCS16; 30% for LCS12 and 35% for Mirena. In the pooled results, these symptoms were recorded only if voluntarily reported by the subjects. LCS16 subjects reported an 8.4% incidence of breast pain and discomfort and LCS12 subjects reported a 6.6% incidence. Therefore, these symptoms in the Mirena group women were probably reported more frequently due to the study methodology.*

Ovarian Cysts

Ovarian cysts were reported as AEs if they were abnormal, nonfunctional cysts and/or had a diameter > 3 cm on ultrasound regardless of the presence or absence of any associated symptoms.

The overall frequency of ovarian cysts in the LCS16 as shown in Table 34 above was 21.3%.

Per protocol, women were discontinued from the studies if they had a persisting ovarian cyst with a diameter of > 5 cm for 3 months or longer. In the LCS16 Efficacy study, the IUS was removed due to an ovarian cyst in 8 women (0.6%) in the LCS16 group and in the phase 2 study, the IUS was discontinued in 2 women in the LCS 16 group.

In the phase 2 study, all ovarian cysts in the LCS16 group were reported as nonserious events and all resolved spontaneously.

In the phase 3 Efficacy study, a total of 3 women reported 4 ovarian cysts as SAE's:

Reviewer Comments

- *Subject 190202: 19 weeks after the start of the study, Subject 190202 had a twisted right ovarian cyst requiring hospitalization and a laparoscopic right salpingo-oophorectomy*
- *Subject 200301: 83 weeks after the start of the study, Subject 200301 developed a left ovarian cyst requiring hospitalization and laparoscopy.*
- *Subject 241511: 43 weeks after the start of the study, Subject 241511 was diagnosed with rupture of a right ovarian cyst, which required inpatient hospitalization. An ultrasound examination confirmed that the right ovarian cyst resolved, but noted "free fluid in the Cul de Sac", and a 2.4 cm left ovarian cyst. The subject required narcotics and the cyst eventually resolved.*
- *In both studies, the frequency of ovarian cysts reported as AEs increased with increasing dose of LNG.*
- *In addition to the MedDRA preferred term "ovarian cyst," ovarian cysts were also reported using MedDRA preferred terms "hemorrhagic ovarian cyst," "ovarian cyst ruptured and "ovarian cyst torsion." If all these preferred terms were included, the overall frequency of ovarian cysts in the LCS16 group was 393 cases (23.1%) as shown in Table 35.*

Table 35 Women with Ovarian Cysts, Preferred Terms, Pooled Data

MedDRA Preferred Term	LCS16 N=1697 (100%) n (%)	LCS12 N=1672 (100%) n (%)
Ovarian cyst	362 (21.3)	207 (12.4)
Hemorrhagic ovarian cyst	21 (1.2)	14 (0.8)
Ovarian cyst ruptured	9 (0.5)	4 (0.2)
Ovarian cyst torsion	1 (<0.1)	0
Any ovarian cyst*	393 (23.1)	225 (13.5)

*Numbers may not sum because a women may have had more than one preferred term listed for a reported AE.
Source: Integrated Analysis. Page 95 of 2364, Table 1.3/7

7.3.4.4 Vascular Disorders

An overview of AEs of the SOC Vascular Disorders for the pooled studies is presented in Table 36 below. Hypertension and varicose veins were the most frequent disorders reported. The frequency of vascular disorders was similar among the treatment groups.

Table 36 Number of Women with Vascular Disorders, Pooled Data

Condition	LCS16 5-Year N=1697 (100%) n (%)	LCS12 3-Year N=1672 (100%) n (%)	Mirena N=256 (100%) n (%)
Any vascular disorder	**33 (1.9)**	**24 (1.4)**	**4 (1.6)**
Hypertension	20 (1.2)	13 (0.8)	3 (1.2)
Varicose vein	8 (0.5)	2 (0.1)	0
Hot flush	3 (0.2)	4 (0.2)	0
Hypotension	2 (0.1)	1 (<0.1)	0
Phlebitis	1 (<0.1)	1 (<0.1)	0
Vascular pain	1 (<0.1)	0	0
Deep vein thrombosis	0	1 (<0.1)	0

Note: A woman may have had more than one vascular disorder.
Source: Summary of Clinical Safety, Page 139, Table 2-34

Two of the women in the pooled LCS16 group had SAEs resulting from hypertension and varicose veins.

Reviewer Comments

- *A 28-year-old woman (Subject 180729) reported mild varicose veins on study day 373. She later reported the varicose veins as moderate in intensity. She was hospitalized to undergo a varicectomy. She recovered and LCS16 was not withdrawn. The event was assessed as being not related to the study drug.*
- *A 33-year-old woman (Subject 242813) completed the extension phase of the study on* (b) (6) *and the LCS16 was removed on that day. On* (b) (6) *a week after removal of the LCS, the subject was admitted to hospital due to severe uncontrolled hypertension. The event was assessed as not being related to the study drug.*
- *Thromboembolic events were identified via the standardized MedDRA queries (SMQ) for the pooled studies (embolic and thrombotic events, arterial, embolic and thrombotic events, venous and embolic and thrombotic events unspecified and mixed). There were no thromboembolic adverse events reported for the LCS16 group in either the LCS16 efficacy study or the phase 2 study.*

Hemostatic Factors

The hemostatic factors VII, VIII, antithrombin III, protein C, and activated protein C (APC) resistance were assessed in blood samples from 61 women in the LCS16 efficacy study only. However, the Applicant stated that a large number of the blood samples had been inappropriately stored (at -18°C for longer than recommended),

which may have led to some degradation. Therefore, no conclusions could be drawn on the changes in hemostatic factors over the course of the study.

Reviewer Comment

- *The Division does not rely upon evaluation of hemostatic factors to draw conclusions about the thrombogenic potential of a hormonal contraceptive.*

7.3.5 Submission-Specific Primary Safety Concerns

Expulsions

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

The frequency of partial and total expulsions is shown below in Table 37.

Table 37 Number of Subjects with Expulsions, Pooled Data

IUS Expulsions	LCS16 5-Year N=1,690* n (%)	LCS12 3-Year N=1,665 n (%)	Mirena N=254 n (%)
Partial expulsion**	37 (2.2)	25 (1.5)	5 (2.0)
Total expulsion***	22 (1.3)	29 (1.7)	0
Partial and total expulsion	59 (3.5)	54 (3.2)	5 (2.0)

*Includes only subjects with a successful insertion
** Defined as an IUS located at least partially in the cervical canal by exam or ultrasound.
*** Defined as an IUS observed in the vagina by exam and/or not observed in the uterine cavity by ultrasound
Source: Integrated Analysis. Page 473, Table 1.1/60

Reviewer Comment

- *The 3.5% LCS16 expulsion rate is similar to that of Skyla and Mirena.*

The probability of an IUS expulsion occurring at 1, 3 and 5 years of use is shown in Table 38.

Table 38 Probabilityof Expulsions by Year, Pooled Data

Month	No. of Subjects	Cumulative Partial/Complete Expulsions	Cumulative Probability of Expulsion (%)
LCS16			
0	1,690	0	0
12	1,414	36	2.26
36	865	50	3.37
48	634	52	3.62
60	184	59	4.80
LCS12			
0	1,665	0	0
12	1,374	29	1.89
36	363	53	3.98
Mirena			
0	254	0	0
12	219	3	1.26
36	100	5	2.20

Source: Integrated Analysis. Page 476, Table 1.1/61

Reviewer Comments

- *Over half of the expulsions (36/59) among women treated with LCS16 had occurred by Month 12 and majority (50/59) by Month 36.*
- *The probability of expulsion was very similar for all three IUSs.*

More partial and total expulsions occurred in parous women than in nulliparous women.

Table 39 LCS16, Partial and Total Expulsions by Parity and Age, Pooled Data

	LCS16-5 Year N=1,690 (%)	
	Partial* and Total Expulsion**	**Total Expulsion** Only**
Overall	**4.80%**	**1.79%**
Parity		
• 0 births	2.50%	0.36%
• ≥ 1 birth	6.10%	2.57%
Age (years)		
• ≤ 25	5.29%	1.48%
• 26-35	4.67%	1.96%

* Defined as an IUS located at least partially in the cervical canal by exam or ultrasound.
** Defined as an IUS observed in the vagina by exam and/or not observed in the uterine cavity by ultrasound
Source: Summary of Clinical Safety, Page 161, Table 4-3 and Integrated Analysis, Pages 482, Tables 1.1/62 through 1.1/67

Reviewer Comments

- *Partial expulsion of the IUS into the cervical canal, or complete expulsion of the IUS into the vagina, will result in a loss of contraceptive efficacy.*

Perforation

The Applicant defined uterine perforation as the partial or complete perforation of the uterus or cervix and can occur during the sounding before insertion, or during the insertion of LCS itself. Uterine perforation may not be diagnosed until sometime later. All perforations were to be reported as SAEs and the woman was to be discontinued from the study treatment.

In the LCS16 Efficacy study, three partial uterine perforations were reported in 3 women in the LCS16 arm. All were assessed as mild or moderate in intensity and all were embedded in the uterine wall. One perforation was diagnosed during the first 3 years of use (Day 722), and two additional partial perforations were diagnosed in the extension phase of the LCS16 Efficacy study.

No perforations were diagnosed in the phase 2 study.

In summary, based on data from the LCS16 Efficacy study, uterine perforations occurred in 1 of 984 subjects (0.1%) of the women during the first 3 years of study treatment and in an additional 2 subjects of 687 (0.3%) during 5 years of study treatment.

Table 40 LCS16, Perforations, FAS, LCS Efficacy Study

Subject #/ Age/ Race/ Parity	AE intensity	AE Onset Study day	Perforation Type	Outcome
160978/ 26 years/ Caucasian Nulliparous	Moderate	Day 722	Myometrial Partial	Recovered, resolved
245930/ 33 years/ Caucasian Multiparous	Moderate	Day 1092 (Ext. phase)	Myometrial Partial	Recovered, resolved
120629/ 25 years/ Caucasian Nulliparous (Prior Cesarean section)	Mild	Day 1271 (Ext. phase)	Myometrial Partial	Recovered, resolved

Source: Integrated Analysis, Page 414 of 745, Table 1.1/54; CSR PH-37274, Page 180 of 1210, Table 14.1/60 Listing 16.2.5/8

Reviewer Comments

- *Only one partial uterine perforation was reported for LCS12 over these trials.*
- *Given the small number of uterine perforations, the assessment of risk factors for perforation cannot be assessed.*

IUD Insertion Ease and Pain

Overall LCS16 IUS insertion was successful in over 96% of all subjects.

Table 41 Number of Successful Insertions, FAS, Pooled Data

Number of Subjects	LCS16 n (%)	LCS12 n (%)	Mirena n (%)
First insertion attempted	1,697 (100)	1,672 (100)	256 (100)
First IUS insertion completed	1,631 (96.1)	1,617 (96.7)	249 (97.3)
First IUS insertion not completed	66 (3.9)	55 (3.3)	7 (2.7)
Second insertion attempted	61 (100)	52 (100)	6 (100)
Second IUS insertion completed	59 (96.7)	48 (92.3)	5 (83.3)
Second IUS insertion not completed	2 (3.3)	4 (7.7)	1 (16.7)

Source: Summary of Clinical Safety, Page 165, Table 4-7

The reasons for the 66 LCS16 failed first insertions in the pooled data were as follows:

- IUS came out immediately after insertion in 25 subjects (37.9%)
- Malfunction of the inserter in 13 subjects (19.7%)
- Cervix too tight in 7 subjects (10.6%)
- IUS became unsterile in 3 subjects (4.5%)
- Position of the uterus in 1 subject (1.5%)
- IUS inserter became unsterile in 1 subject (1.5%)
- Small uterus in 1 subject (1.5%)
- Vasovagal attack in 1 subject (1.5%)

Reviewer Comments

- *Possibly because of this number of failed insertions, the Applicant decided to modify the IUS inserter after the study was complete, (b) (4) he insertion procedure itself using the modified inserter is unchanged. This modified inserter (which the Applicant has named the (b) (4) inserter) is the to-be-marketed inserter.*
- *The (b) (4) inserter is discussed in Section 7.3.5 of this review.*

Local anesthesia was used for insertion in 147 women (8.7%), with nulliparous women receiving local more commonly than parous women. Pre-insertion analgesics were given to 572 women (34.7%).

The investigators assessed the insertion procedure of the LCS16 and LCS12 IUSs as easy in approximately 90% of women, and the insertion procedure for Mirena was assessed as easy in approximately 86% of women. Insertion in parous women was easier in all treatment groups, and insertion was assessed easier with increasing age of

the women. The insertion of Mirena was rated as more difficult than the insertion of LCS12 or LCS16.

Reviewer Comment

- *The proposed duration of action for LCS16 is 5 years, which is the same as Mirena. The fact that it is less difficult to insert may make it more attractive to use for both providers and patients.*

IUD Removal Ease and Pain

In the LCS16 Efficacy study, over 70% of LCS16 users chose to keep their IUS for another two years in the extension study. The investigators assessed the removal of LCS16 (after up to 5 years of treatment) as easy in 1,405/1,589 women (88.4%). Removal was assessed as very difficult in this group in 34 (2.1%). Parity did not affect the assessment, with approximately equal numbers of easy removals in parous and nulliparous women, although nulliparous women reported more pain with removal than parous women.

Return to Fertility

All women in both studies were asked to contact the site if they became pregnant within 3 months or within 12 months of prematurely discontinuing the study if they wished to conceive. In addition, all women in both studies were contacted at 3 months and 12 months after the end of study treatment to record any pregnancies that had taken place after the LCS removal and to collect data on return-to-fertility.

In the LCS16 Efficacy study, a total of 179 women out of the 1,452 in the LCS16 group discontinued the LCS16 treatment (including the optional extension phase) because of a wish for pregnancy. Of these, follow-up information was available for 163 women (91.1%). A total of 116 of these women (71.2%) became pregnant during the 12-month follow-up.

In the phase 2 study, data were available for a total of 29 women who had discontinued the study drug for wish of pregnancy (LCS16: 11, LCS12: 7 and Mirena: 11 women), of whom 25 had conceived during the 12-month follow-up (8 in the LCS16 group [72.7%], 6 in the LCS12 group, and all 11 in the Mirena group).

Reviewer Comment

- *Overall, 124 of the 174 women (71%) in the LCS16 group who discontinued treatment to get pregnant and had follow-up became pregnant. Based on these limited data, there is no evidence to suggest that return to fertility following use of LCS16 is impaired.*

Data to support use of the (b) (4) inserter

The phase 2 and phase 3 clinical studies used to support this NDA application did not use the planned to-be-marketed (b) (4) inserter. While these studies were being performed, the (b) (4) Inserter was being developed (b) (4)

[redacted] Because the proposed to-be-marketed [redacted] inserter was not used in the phase 2 and phase 3 clinical trials, the Division requested more data to support the safety of this inserter during the review of the Skyla NDA. On January 9, 2013, after a review of the submitted inserter data, the Division concluded the [redacted] inserter was safe and effective and approved the Skyla NDA application for prevention of pregnancy for up to 3 years, with labeling describing use of the [redacted] inserter.

For the to-be-marketed LCS16 IUS, the [redacted] inserter will also be used. This inserter has the same design and the same dimensions as the inserter marketed with LCS12. With the [redacted] inserter, [redacted] The insertion procedure itself is unchanged.

The safety data supporting the use of the [redacted] inserter with LCS16 is based on three studies in which LCS12 was inserted using the [redacted] Inserter:

1. Protocol 13362: LCS12 Profiling 1 Study (LCS12 vs Yasmin),
   - "A multicenter, randomized, open-label, parallel-group study to evaluate user satisfaction in young nulliparous and parous women (18 to 29 years of age) using LCS12 compared with women using a combined oral contraceptive containing 0.030 mg ethinyl estradiol and 3 mg drospirenone (Yasmin) over a period of 18 months."
   - This study was conducted at 42 centers in Europe and the United States.
   - FAS=279
   - Insertion attempts: 282
   - Successful insertions: 279 (98.9%)

2. Protocol 13363: LCS12 Profiling 2 Study (LCS12 vs Nexplanon)
   - "A multicenter, open-label, randomized, controlled parallel-group study to assess discontinuation rates, bleeding patterns, user satisfaction and adverse event profile of LCS12 in comparison to an etonogestrel subdermal implant (Nexplanon) over 12 months of use."
   - This study was conducted at 38 centers in Australia and 5 European countries.
   - FAS=382
   - Insertion attempts: 386
   - Successful insertions 378 (97.9%)

3. Protocol 14371: LCS12 Adolescent Study Protocol
    - "A multicenter, single arm study to assess the safety, efficacy, discontinuation rate and pharmacokinetics of LCS12 in adolescent women less than 18 years of age for 1 year."
    - This study was conducted at 36 centers in Australia and 8 European countries.
    - FAS=304
    - A total of 302 of the subjects were less than 18 years of age.
    - Insertion attempts: 310
    - Successful insertions: 303 (97.7%)

Reviewer Comments

- *Data presented for the LCS12 Profiling 1 study includes the optional 18-month extension phase, whereas the data of the LCS12 Profiling 2 and the LCS12 Adolescent study refer to the 1-year main studies excluding the optional 2-year extensions.*
- *The* (b) (4) *inserter data obtained from the above studies was obtained using LCS12 (Skyla). No studies were done with LCS16. However, the dimensions of the Skyla IUS are virtually identical to LCS16, and that the proposed* (b) (4) *inserter to be used with LCS16 is identical in all relevant aspects to the inserter used with Skyla.*

In total, insertion was attempted in 965 women (FAS, pooled population) and for 960 women (98.2%) the insertions of LCS12 with the (b) (4) inserter were successful. The insertion was successful at the first attempt in 948 women and in 12 women at the second attempt. A total of 17 insertions failed at the first attempt and 1 at the second. Reasons for unsuccessful insertion included 'IUS came out immediately after insertion' (3 women), pain (2 women), and 'unable to pass IUS through internal os (twice in the same woman). Other reasons were reported only once.

Table 42 LCS12 (b) (4) Insertion Studies

	13362 LCS12 Profiling 1 Study	13363 LCS12 Profiling 2 Study**	14371 Adolescent Study	Pooled
Randomized	282	385	304	971
FAS*	279	382	304	965
Nulliparous Subjects	233 (83.5%)	301 (78.8%)	297 (97.7%)	831 (86.1%)
First insertion successful	276/279 (98.9%)	375/382 (98.2%)	297/304 (97.7%)	948/965 (98.2%)
Reasons for IUS insertion failure	-"inserter failed" -"slider malfunction" -"strings stuck to scissors when cutting and pulled IUS out"	-"IUS stayed linked to the inserter and came out with the inserter" -"unable to pass IUS through internal os" -"device failed to deploy"	-"during the cutting off the threads the thread stick behind the scissors so he had to use a new IUD" -"dislocation of LCS" -"pain during dilatation" -"IUS was descended from fundus while pulling the slider out"	
Second insertion Successful/Failed	3/0	3/1 -"Unable to pass IUS through internal os"	6/0	12/1 -Stenotic os

* The LCS12 FAS includes all women with at least one insertion attempt (successful or unsuccessful). A total of 6 randomized women were not included in the FAS as they never had an insertion attempt.
** In the Profiling 2 Clinical Study Report, only women with successful insertions were included in the FAS.
Source: Adapted from Summary of Clinical Safety, Page 204, Table 5-9

Overall, no dilatation was needed for more than 60% of the women treated with LCS12 using the (b) (4) inserter. If dilation was needed, it was mainly performed before the insertion attempt (18.9% of all women). A trend towards higher frequency of dilatations needed in nulliparous women was noted.

Overall, 8.8% of the women had a paracervical block performed before the insertion procedure was started and in 1 woman when the insertion proved to be difficult. There was a trend towards a higher frequency of utilization of a paracervical block in the Adolescent Study (11.2%) compared to the subjects in the LCS12 Profiling 1 and 2 studies, (6.8% and 8.4%, respectively). Paracervical block was used more often in nulliparous (82 women) than for parous women (3 women),

Analgesics were administered in more than a third of the pooled population, most commonly before the insertion procedure (36.7%). Analgesics (before insertion attempt) were generally given more frequently in the adolescent population (55.3%)

compared to the adult population (15.4% and 37.4% in the LCS12 Profiling 1 and 2 studies, respectively). Again, analgesics were used more often in nulliparous women (40.8%, before insertion) when compared to parous women (16.1%).

Table 43 LCS12 (b) (4) Insertion Studies

	13362 LCS12 Profiling 1 Study	13363 LCS12 Profiling 2 Study**	14371 Adolescent Study	Pool
Randomized	282	385	304	971
FAS*	279	382	304	965
Nulliparous Subjects	233 (83.5%)	301 (78.8%)	297 (97.7%)	831 (86.1%)
First insertion successful	276/279 (98.9%)	375/382 (98.2%)	297/304 (97.7%)	948/965 (98.2%)
Reasons for IUS Malfunctions	-"inserter failed" -"slider malfunction" -"strings stuck to scissors when cutting and pulled IUS out"	-"IUS stayed linked to the inserter and came out with the inserter" -"unable to pass IUS through internal os" -"device failed to deploy"	-"during the cutting off the threads the thread stick behind the scissors so he had to use a new IUD" -"dislocation of LCS" -"pain during dilatation" -"IUS was descended from fundus while pulling the slider out"	
Second insertion Successful/Failed	3/0	3/1 -"Unable to pass IUS through internal os"	6/0	12/1 -Stenotic os

* The LCS12 FAS includes all women with at least one insertion attempt (successful or unsuccessful). A total of 6 randomized women were not included in the FAS as they never had an insertion attempt.
** In the Profiling 2 Clinical Study Report, only women with successful insertions were included in the FAS.
Source: Adapted from Summary of Clinical Safety, Page 204, Table 5-9

Reviewer Comments

- *The (b) (4) inserter for LCS16 is similar to the approved Skyla inserter and the approved Mirena inserter. The insertion procedure is also the same.*
- *The data submitted by Bayer from these trials were reassuring regarding the safety and efficacy of this inserter. The data indicate that this inserter appears to be as effective and safe as that used in the clinical trials. The modifications found in the (b) (4) inserter do not represent a safety concern for LCS16 use.*
- *See Section 7.7.1, the 4-Month Safety Update Report for updated information regarding these studies.*

- *The 97-98% successful LCS12 insertion rate using the (b) (4) inserter is equal to or better than the 96-97% successful insertion rate in the pooled clinical trials, which did not utilize the (b) (4) inserter.*

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The most frequently reported AEs were reported using MedDRA (version 17.1).

From a total of 1,697 women (pooled data) treated with LCS16 in the LCS16 Efficacy Study and the phase 2 Study, 1,506 women (88.7%) reported at least 1 AE during the 5-year duration of treatment.

Drug-related adverse events (defined as those AEs assessed by the investigator as possibly, probably, or definitely related to the study drug) occurred in 966 (56.9%) subjects in the pooled LCS16 group.

Table 44 Adverse Event Profile, Pooled Data

	LCS16 5-Year n (%)	**LCS12 3-Year n (%)**
Total no. (%) of women	**1697 (100)**	**1672 (100)**
Any AE no. (%) women]	1506 (88.7)	1402 (83.9)
Drug-related	966 (56.9)	872 (52.2)
Maximum intensity -mild -moderate -severe	 389 (22.9) 786 (46.3) 316 (18.6)	 366 (21.9) 738 (44.1) 294 (17.6)
Maximum intensity of study drug related AEs -mild -moderate -severe	 406 (23.9) 429 (25.3) 130 (7.7)	 335 (20.0) 405 (24.2) 128 (7.7)
Total deaths • drug- related deaths	2* 0	0 0
Serious AEs -Drug related SAEs	98 (5.8) 22 (1.3)	78 (4.7) 22 (1.3)
Discontinuation due to AEs	375 (22.1)	361 (21.6)
Discontinuation due to SAEs	27 (1.6)	15 (0.9)

***** A 20-year-old woman committed suicide, LCS16 Efficacy Study, subject no. 210112 and a 33-year-old woman had an accident and died after major trauma, LCS16 Efficacy Study, subject no. 180709.

Reviewer Comment

- *The type and intensity of AEs were similar between the LCS groups.*

The most common AEs reported in the pooled LCS16 group were ovarian cyst (21.3%) acne (14.1%), and headache (12.3%). The most frequent AEs that were assessed by the investigator as drug-related were ovarian cyst (14.7%), acne (12.0%) and pelvic pain (5.5%).

Table 45 LCS16 Most Frequent Adverse Events, Pooled Data

Adverse Event	LCS16 5-Year N=1697 n (%)	LCS12 3-Year N = 1672 (100%) n (%)
Most Frequent AEs (>7% in the LCS16 group)		
Any AE	**1506 (88.7)**	**1402 (83.9)**
Ovarian cyst	362 (21.3)	207 (12.4)
Acne	240 (14.1)	227 (13.6)
Headache	209 (12.3)	195 (11.7)
Cervical dysplasia	154 (9.1)	112 (6.7)
Pelvic pain	136 (8.0)	100 (6.0)
Dysmenorrhea	135 (8.0)	144 (8.6)
Abdominal pain	123 (7.2)	117 (7.0)
Most Frequent Drug-Related* AEs (≥2.5% in the LCS16 group)		
Any drug-related AE	**966 (56.9)**	**872 (52.2)**
Ovarian cyst	249 (14.7)	124 (7.4)
Acne	203 (12.0)	206 (12.3)
Pelvic pain	93 (5.5)	70 (4.2)
Dysmenorrhea	91 (5.4)	110 (6.6)
Headache	82 (4.8)	74 (4.5)
Weight increased	79 (4.7)	61 (3.6)
Vaginal hemorrhage	76 (4.5)	75 (4.5)
Breast pain	54 (3.2)	38 (2.3)
Breast discomfort	53 (3.1)	50 (3.0)
Abdominal pain	50 (2.9)	61 (3.6)
Abdominal pain lower	48 (2.8)	38 (2.3)
Abdominal distension	42 (2.5)	45 (2.7)

Note: A woman may have had more than one AE
* Missing, possible, probable, and definite for drug relationship (as assessed by the investigator) is counted as drug-related.
Source: Summary of Clinical Safety, Page 89, Table 2-9

Reviewer Comments

- *With the exception of the ovarian cysts, the AEs were generally similar between the two LCS groups. Ovarian cysts were almost twice as common in*

the LCS16 group; however, the 21.3% for LCS16 group occurred over a period of 5 years rather than 3 years.

- *I agree that the above ARs could be drug-related.*

7.4.2 Laboratory Findings

Clinical laboratory evaluations were performed in both studies (LCS16 Efficacy study and the phase 2 study). Clinical laboratory parameters were assessed at screening, Month 36, and the end of the 2-year extension period. Laboratory evaluations included urinalysis, clinical chemistries, liver enzymes, hematology, lipids, and hemoglobin A1C.

These safety laboratory evaluations were generally unaffected by treatment with LCS16.

Laboratory values higher or lower than the normal range (in women with normal baseline values) that occurred in more than 4% of women in the LCS16 pool are summarized below.

Table 46 LCS16 Lab Values Outside the Normal Range in 4% of Women, Pooled

	N*	LCS16 5-yr n (%) **
Abnormally high laboratory values		
Hematocrit	1,528	136 (8.9)
Gamma glutamyl transferase	1,526	79 (5.2)
Triglycerides	1,422	70 (4.9)
Cholesterol-HDL	1,520	97 (6.4)
Abnormally low laboratory values		
Hemoglobin	1,405	73 (5.2)
Triglycerides	1,500	60 (4.0)
Cholesterol-HDL	1,460	97 (6.6)

*Number of women with at least one normal or lower than normal laboratory assessment at baseline who also had 1 valid laboratory value after the start of treatment.
** number of women with at least one high laboratory assessment after the start of treatment who had a normal or lower than normal laboratory assessment at baseline.
Source: Summary of Clinical Safety, Page 154, Table 3-1

Reviewer Comment

- *For both studies, clinically relevant laboratory abnormalities were not observed.*

7.4.3 Vital Signs

Vital signs, including weight, systolic and diastolic blood pressure, and heart rate, were analyzed at screening, Month 12, Month 24 and end of study (Month 36). Additionally, for those who did take part in the extension of the LCS16 Efficacy Study, measurements were performed at Month 48 and end of extension.

Height was measured and the BMI was calculated at the screening visit. No relevant differences (i.e., change from baseline to end of study) in mean weight, mean systolic blood pressure, mean diastolic blood pressure, or mean heart rate were found for the LCS16 group during up to 5 years of treatment.

Table 47 LCS16 Group, Mean Change in Body Weight and Vital Signs, Pooled Data

	LCS16 5-Year n=682 to 693/1,697
	Mean (SD) Change from Baseline to Last Measurement (up to End of Extension Study)
Body weight (kg)	2.2 (7.4)
Systolic blood pressure (mm Hg)	1.8 (11.8)
Diastolic blood pressure (mm Hg)	0.7 (9.1)
Heart rate (beats/minute)	0.2 (10.7)

Source: Summary of Clinical Safety, Page 157, Table 4-1

7.4.4 Electrocardiograms (ECGs)

Electrocardiograms were not performed for either the LCS16 Efficacy Study or the phase 2 Study.

7.4.5 Special Safety Studies/Clinical Trials

No special safety studies were performed for this submission.

7.4.6 Immunogenicity

Not applicable for this submission.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

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

7.5.2 Time Dependency for Adverse Events

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

7.5.3 Drug-Demographic Interactions

This product is indicated for use only in women of childbearing age. No other special populations were studied.

7.5.4 Drug-Disease Interactions

No drug-disease interactions were studied.

7.5.5 Drug-Drug Interactions

No drug-drug interaction studies were performed for this NDA application. Drug-drug interactions are not expected due to the local mechanism of action of this product.

7.5.6 Bone Mineral Density

Bone mineral density (BMD) was measured at the lumbar spine and total hip using dual-energy x-ray absorptiometry (DEXA) in a subgroup of 205 women (LCS16: 103 women and LCS12: 102 women) in the LCS16 Efficacy study only. A total of 62 of the women in this subgroup who were assigned to LCS16 entered the extension study.

Baseline measurements were compared with measurements at Month 12, Month 24, Month 36 (or premature discontinuation), Month 48, and end of extension, and percentage change was calculated.

There was a slight increase in mean BMD at both anatomic sites at all three post-baseline visits in both treatment groups until Year 3. No difference was seen between the two treatment groups. For the LCS16 treatment group, the mean BMD increase in the lumbar spine at the end of 3 years was 0.03% and in the total hip was 0.02%.

Bone mineral density was not assessed in the phase 2 study.

Table 48 Bone Mineral Density, LCS16 Efficacy Study

	# Subjects/ Mean BMD at Baseline	Subjects/ Mean BMD EOS/Month 36	Change From Baseline	Subjects/ Mean BMD EOS/Month 60	Change From Baseline	SD
LCS16						
Lumbar spine	103 / 1.1793	71 /1.2123	0.0293	37/ 1.2152	0.0256	0.0395
Total hip	102 / 1.0207	71 /1.0353	0.0158	37/ 1.0457	0.0165	0.0371
LCS12						
Lumbar spine	102 / 1.1829	80 / 1.2118	0.0199	-	-	-
Total hip	102 / 1.0404	80 / 1.0466	0.0107	-	-	-

Source: Clinical Study Report PH-37274 Page 409, Table 10-27; Summary of Clinical Safety, Page 183, Table 4-23

Reviewer Comment

- *In the LCS16 group, there was no decrease in mean bone mineral density measurements over the whole observation period of 5 years.*

7.5.7 Endometrial Histology

Endometrial histology was studied at baseline and once a year in a subset of 29 women treated with LCS16 (15 in extension group and 14 in the 3-year group). There was a decrease in estrogen effects and an increase in progesterone effects in subjects treated with LCS16. The histological evaluation of the endometrium at Years 1-5 showed normal findings for all subjects assessed.

- At Month 12, and at Month 24, endometrium was secretory in all subjects
- At Month 36, the end of the 3-year study, the endometrium was secretory in 22/23 women and proliferative in 1/23 subjects.
- At Month 48 and at the end of the extension study, the endometrium was secretory in all subjects.

Reviewer Comment

- *The endometrial histological findings revealed only the expected effects based on LNG's pharmacology.*

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

No human carcinogenicity trials were indicated or performed.

7.6.2 Human Reproduction and Pregnancy Data

Pregnancy
The use of LCS16 during an existing or suspected pregnancy is contraindicated and if a woman becomes pregnant, removal of the IUS is recommended. Based on the available post-marketing data for other LNG IUSs, no trend towards specific anomalies has been observed with Skyla or Mirena in cases where pregnancy continued to term with these two LNG-IUSs in place

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

Reviewer Comments

- *LNG is transferred to the infants' circulation via the breast milk; this is noted in labeling for Mirena and other LNG contraceptives, and will be labeled for LCS16.*
- *In general, no adverse effects have been found from the small amounts of progestins that pass into the breast milk of nursing mothers. There appears to be no deleterious effect on infant growth or development when using any progestogen-only method after six weeks postpartum.*
- *The LNG-IUS does not affect the quantity or quality of breast milk, so LCS16 can be used by nursing mothers.*

7.6.3 Pediatrics and Assessment of Effects on Growth

Mirena labeling states that no adverse effects on growth or development has been found in infants' breastfed by users of progestin-only contraceptives.

7.6.3.1 Pediatric Research Equity Act (PREA)

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

Based on the intended use of the product, Bayer proposed to address the PREA requirements for LCS16 as follows:

- Because contraception is not needed and LCS16 will not be indicated in premenarchal patients, Bayer requested a partial waiver from pediatric study requirements for these patients.
- Because the reproductive physiology of post-pubertal adolescent females < 17 years of age is similar to that of other women of reproductive age, Bayer requested that the PREA requirements for post-menarchal pediatric patients be deemed fulfilled by extrapolation of adult data.

However, an assessment of the safety and efficacy of this product for the pediatric population was not required under PREA because LCS16 did not represent a new active ingredient, a new dosage form or regimen of levonorgestrel or a new route of administration.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Not applicable for this submission.

7.7 Additional Submissions / Safety Issues

7.7.1 The 4-Month Safety Update Report

A 4-Month Safety Update Report (PSUR) was received on March 16, 2016 and covered the period from July 16, 2015 through January 15, 2016. Since the July 15, 2015 cut-off date used for the LCS16 NDA, no new studies have been initiated; consequently, no new safety data for LCS16 are presented in this Safety Update Report.

At the time of the LCS16 NDA submission, the LCS12 Profiling 1 study using the (b) (4) (b) (4) inserter had already been completed. The other two LCS12 studies with the (b) (4) inserter (the LCS12 Profiling 2 study and the LCS12 Adolescent Study) that were initially identified as ongoing in the LCS16 NDA application were subsequently completed. Safety information from these studies was provided in the Safety Update Report. (See Section 7.3.5 Data to support use of the (b) (4) inserter.)

Table 49 Ongoing (b) (4) inserter studies with LCS12

Study Centers Location	Design Duration	Study Population	Number of Subjects	Study Objective
Phase 3 LCS12 Profiling 2 Study (LCS12 vs Nexplanon), Protocol 13363				
43 centers: Australia Finland France Norway Sweden UK	-Multicenter, open-label -2-arm -12 months, with an extension for up to 3 years -(b) (4) inserter[1]	-Healthy, 18-35 yrs -nulliparous or parous	-LCS12: 385 -Nexplanon: 381 -FPFV: 9/15/11 -LPLV: 4/30/15	-To demonstrate that discontinuation rates in women using LCS12 are not higher than those seen in women using etonogestrel subdermal implants over 12 months
Phase 3 LCS12 Adolescent Study, Protocol 14371				
39 centers: Austria Belgium Denmark Finland Germany Netherlands Norway US	-Multicenter, open label, single-arm -12 months, with an extension for up to 3 years (b) (4) inserter[1]	-Healthy, menarche to 18 yrs -nulliparous or parous adolescents with regular menses	-LCS12: 304 -FPFV: 9/26/11 -LPLV: 5/28/15	-To assess the safety of LCS12 in adolescents over 1 year of treatment, including the insertion and removal procedures.

[1] These studies (protocols 13362, 13363, and 14371) were performed using the modified IUS inserter ("(b) (4)" inserter), which is of the same design as will be used for the marketed product.
[2] First patient, first visit
Source: 4-Month Safety Update Report, Page 10, Table 1

Reviewer Comments

- *The design and dimensions of the modified LCS12 and LCS16 inserters are identical so these studies are relevant to support the use of the (b) (4) inserter for LCS16; they are discussed in more detail below.*

- *The submitted 4-Month Safety Update covering the period from July 16, 2015 to January 15, 2016 does not document any unexpected safety findings for LCS16.*

7.7.1.2 LCS12 Profiling 2 Study (Protocol 13363)

This was a phase 3 multicenter, open-label, randomized, controlled parallel-group study, which was initiated in September 2011 and utilized the (b) (4) inserter. The study assessed discontinuation rates (primary objective), bleeding patterns, user satisfaction and the AE profile of LCS12 in comparison to an etonogestrel (ENG) subdermal implant (Nexplanon) over 12 months in women 18 to 35 years of age with an optional 2-year extension phase for the subjects in the LCS12 group. The women in the ENG implant group had the option to continue the implant use under standard care for up to 3 years.

The one-year primary part of the study was completed and the study report (CSR PH-37273) was included in the NDA submission. The clinical part of the extension phase was completed at the time of the NDA submission, but the analyses were still ongoing. Results from the extension phase of the study are included in the 4-month Safety Update Report and include the safety results for up to 3 years of LCS12 treatment.

A total of 766 subjects were randomized in this study – 385 to the LCS12 arm and 381 to the ENG implant arm. During the first year of the study, 81 subjects (21.0%) in the LCS12 group and 102 subjects (26.8%) in the ENG implant group prematurely discontinued the study treatment.

Of the 304 subjects in the LCS12 arm completing Year-1, 283 subjects entered the optional extension phase, with 199 subjects (70.3%) completing all 3 years of the study. A total of 84 subjects (29.7%) discontinued during the 2-year extension phase; almost half of those subjects (41, 14.5%) due to AEs. There were 3 discontinuations due to pregnancies in the extension phase.

A total of 382 subjects were included in the FAS for the entire 3-year study period. Mean duration of exposure to the LCS12 was 2.11 WY (SD: 1.04; range 0 – 3.1 years); total exposure was 803.42 WY. The average age of the subjects was 24.9 years. A total of 74.2% of the subjects were nulliparous.

A total of 98 subjects (25.7%) discontinued study treatment due to TEAEs; 4 subjects (1.0%) due to serious TEAEs (biochemical pregnancy (defined as a very early pregnancy where secretion of beta HCG has occurred without clinical signs or symptoms of pregnancy), ruptured ectopic pregnancy, pregnancy of unknown location, and ectopic pregnancy with contraceptive device).

The most frequently (i.e., more than 5% in the LCS12 treatment group) reported AEs by

MedDRA preferred term over the entire 3-year treatment period (N=382) were as follows:

- Dysmenorrhea in 137 women (35.9%)
- Cervical dysplasia in 64 women (16.8%)
- Uterine spasm in 61 women (16.0%)

A total of 18 subjects (4.7%) experienced SAEs, of which 5 subjects (1.3%) had events that were considered drug-related. There was 1 death ("completed suicide") reported during the first year of the study, which was not related to the study treatment. No further deaths were reported during the extension phase.

A total of 5 device expulsions (1.3%) were reported (3 partial expulsions during the first year and 2 total expulsions during the extension phase). No uterine perforations were reported during the entire 3-year treatment period. A total of 3 subjects had suspected PID (two of these were in the extension phase). A total of 3 subjects with endometritis were reported in the extension phase.

There were a total of 6 pregnancies in the LCS12 group during the entire study, 3 of which occurred during the first year of the study (1 intrauterine pregnancy, 1 ectopic pregnancy, and 1 biochemical pregnancy) and 3 pregnancies during the 2-year extension phase (1 intrauterine pregnancy, 1 ruptured ectopic pregnancy, and 1 pregnancy of unknown location).

Reviewer Comments

- *This updated information from a study using the (b) (4) inserter did not document any new or unexpected safety concerns.*
- *The Applicant justified the high rate of cervical dysplasia (16.8%) by stating that the study population consisted of young sexually active women who received a protocol-defined annual Pap smear. Without a control group, it is difficult to assess the clinical significance of the 16.8%.*
- *Subject 13363-360030028 committed suicide during the first 5 months on LCS12. She had a history of a "compulsive disorder" from February, 2010 to 2012 treated with Effexor. There was no documented evidence of preexisting depression or other psychiatric illness.*

7.7.1.3 LCS12 Adolescent Study (Protocol 14371)

This was a phase 3 study initiated in Europe in September 2011 to investigate the safety of LCS12 in users between menarche and the age of 18. The focus of this study was to assess AEs, bleeding patterns, discontinuation rates, ease and pain of insertions and removals, expulsion risks and adequate counseling in the adolescent population. The treatment duration was one year with an option to continue LCS12 use and observation in the study up to three years.

The clinical part of the extension phase was completed at the time of the NDA submission, but the data analyses were still ongoing. The final study results of the extension phase (CSR PH-38454) were included in the 4-month Safety Update Report.

Of the 343 subjects enrolled in the 1-year treatment phase, 304 were included in the FAS (i.e., subjects with at least 1 insertion attempt), and 253 subjects (83.2%) completed the first year. Of those, 220 subjects entered the optional 2-year extension phase with 173 subjects (78.6%) completing all 3 years of the study. A total of 47 subjects discontinued during the 2-year extension phase; more than half of the subjects (25) due to AEs.

All 304 FAS subjects were included in the safety analyses for the 3-year study period. Total exposure to the LCS12 was 670.79 WY during the study. The majority of the subjects were white (97.7%) with a mean age of 16.2 years. The age range was 12-18 years, fulfilling the study inclusion criteria. The mean BMI was 22.1 kg/m^2. Most subjects (97.7%) were nulliparous.

A total of 87.8% subjects experienced at least 1 AE and 70 subjects (23.0%) discontinued due to AEs.

The most frequently (i.e., more than 5% in the LCS12 treatment group) reported AEs by MedDRA preferred term over the entire 3-year treatment period (N=382) were as follows:

- Dysmenorrhea in 85 women (28.0%)
- Pelvic pain in 65 women (21.4%)

The most common drug-related AEs leading to study drug discontinuation included mainly bleeding disorders, such as:

- Vaginal hemorrhage (8 subjects, 2.6%)
- Menorrhagia (4 subjects, 1.3%)
- Uterine hemorrhage (2 subjects, 0.7%)
- Device expulsion (15 subjects, 4.9%)
- Pelvic pain (12 subjects, 3.9%)
- Dysmenorrhea (9 subjects, 3.0%)
- Acne (7 subjects, 2.3%)

A total of 14 subjects (4.7%) reported at least one SAE, one of which was a pregnancy. This subject had an early spontaneous abortion after completion of 3 years (1085 days) of study treatment.

No pregnancies occurred in Year 1 of the study but there were 2 pregnancies during the extension phase; in both cases the LCS12 was *in situ*.

Over the entire study period, 26 subjects (8.6%) had ovarian cysts reported as an AE and 15 subjects (4.9%) experienced LCS12 expulsions, including 2 subjects (0.7%) with total expulsions during the entire study; the majority (10 subjects [3.3%]) occurred during the first year. No ectopic pregnancies or uterine perforations occurred during this study.

A total of 3 cases of endometritis were reported during the first year with no new cases during the extension phase. There was 1 subject with suspected PID that occurred during the extension phase.

The investigators assessed almost all LCS12 removal procedures as "easy" (97.2%) and the majority of subjects (87.1%) experienced either no or mild pain during the removal. There was 1 total expulsion and 4 partial expulsions that occurred during the extension phase.

Reviewer Comments

- *This study was conducted in accordance with the Pediatric Investigation Plan as approved by the European Medicines Agency Pediatric Committee.*
- *No uterine perforations were reported during the 2-year extension period in either of the ongoing studies.*
- *Data from this study did not document any new or unexpected safety concerns regarding the* (b) (4) *inserter and supported safety and efficacy in the adolescent population.*

8 Postmarket Experience

No commercial marketing experience has been obtained for LCS16 because this product has not yet been marketed in any country.

Reviewer Comment

- *Bayer submitted an EU Marketing Application for LCS16 on November 16, 2015. Some comments were received regarding Environmental Risk Assessment* (b) (4)

9.1 Literature Review/References

1. Gemzell-Danielsson K. A randomized, phase II study describing the efficacy, bleeding profile, and safety of two low-dose levonorgestrel-releasing intrauterine contraceptive systems and Mirena, Fertil Steril 2012;97:616-22

2. Apter Dan, MD, Ph.D. et al., Pharmacokinetics of two low-dose levonorgestrel-releasing intrauterine systems and effects on ovulation rate and cervical function: pooled analyses of phase II and III studies, Fertil Steril 2014;101:1656-62

Reviewer Comment

- *These articles report on the findings of the phase 2 and the 3-year phase 3 clinical studies.*

9.2 Labeling Recommendations

Labeling is currently under review. The proposed label is undergoing revisions in order to better harmonize with current Mirena, Skyla and Liletta labeling. As of this date, no major labeling issues are anticipated.

9.3 Advisory Committee Meeting

No Advisory Committee Meeting was indicated or held.

10 Appendices

Appendix 1 Schedule of Assessments, LCS16 Efficacy Study (PH-37274)

Assessment / event	Pre-treatment		Treatment							End of Study 3-yrs
Visit	1	2	3	4	5	6	7	8	9	10
Months	Screening	Baseline	3	6	9	12	18	24	30	36
Med/surg, gyn. and menstrual hx	●									
Test for Chlamydia	●									
Randomized treatment allocation, LCS insertion		●								
Vitals, weight, height at screening	●					●		●		●
General physical examination	●									●
Gynecological examination	●	●	●	●	●	●	●	●	●	●
Vaginal ultrasound	●	●	●	●	●	●	●	●	●	●
Pap smear	●					●		●		●
Safety laboratory tests	●									●
Serum pregnancy test	●	●								●
Prior and concomitant medication	●	●	●	●	●	●	●	●	●	●
Adverse events			●	●	●	●	●	●	●	●
LCS insertion ease and pain		●								●
Serum sample for LNG/SHBG[5]			One sample per subject at one of visits 3-10							
Concomitant contraception			●	●	●	●	●	●	●	●
Diary dispensed		●								
Diary pages collected			●	●	●	●	●	●	●	●
Unblinding of LCS16 subjects/ info. on study extension to 5 yrs									●	
End of study medication / end of study / continuation										●

Source: CSR PH-37274, Page 25, Table 7-2

Appendix 2 Schedule of Assessments, LCS16 Efficacy Study Extension Phase

Assessment / event	End of 3 year study	Entry to extension LCS16	Extension for LCS16			End of study 5 years
Visit	**Visit 10**	**Visit 10**	**11**	**12**	**13**	**14**
Months	36	36	42	48	54	60
Initiation / subject characteristics						
Discussion of extension phase		●				
Distribution of subject information		●				
Informed consent		●				
Safety						
Vital signs and weight	●	●		●		●
General physical examination	●	●				●
Gynecological examination	●	●	●	●	●	●
Breast palpation	●	●		●		●
Vaginal ultrasound	●	●	●	●	●	●
Cervical smear	●	●		●		●
Safety laboratory tests	●	●				●
Pregnancy test	●	●		●		●
Concomitant medication	●	●	●	●	●	●
Adverse events	●	●	●	●	●	●
LCS removal ease and pain	●					●
Other						
Serum sample for LNG/SHBG4	1 additional sample per subject at one of visits 10 – 14					
Concomitant contraception	●	●	●	●	●	●
Need of contraception	●	●	●	●	●	●
Diary dispensed		●				
Diary pages collected	●	●	●	●	●	●
End of study medication / end of study / continuation	●	●				●
User-satisfaction questionnaire	●	●				●

Source: CSR PH-37274, Page 26, Table 7-3

Appendix 3 Schedule of Substudy Assessments, LCS16 Efficacy Study

Assessments			Treatment											End of Study
Study visit	1	2					3	4	5	6	7	8	9	10
Months	SC*	BL**					3	6	9	12	18	24	30	36
Days			1	3	7	14								
Ovarian and cervical function (S1)							a 6-week period during 2nd half of each study year							
Endometrial biopsy (S2A)		2A	At baseline and once a year at Months 12, 24, 36, 48 and End of Study.											
Hemostasis (S2B)		2B												
Serum SHBG and LNG (S3)		S3	S3	S3	S3	S3	S3	S3	S3	S3	S3	S3	S3	S3
Bone mineral density (S4) + pregnancy test		S4								S4		S4		S4

*SC: Screening
**BL: Baseline
Source: Protocol 310442, LCS16 Efficacy Study,

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

/s/

RONALD J ORLEANS
09/14/2016

LISA M SOULE
09/14/2016
I concur with Dr. Orleans' conclusions and recommendation for approval of NDA 208-224.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 208224	**Applicant: Bayer Healthcare**	**Stamp Date: 11/18/ 2015**
Drug Name: LCS16	**NDA/BLA Type: 505(b)(1) Standard Review**	**PDUFA Date: 9/18/2016**

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

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic common technical document (eCTD).	X			Electronic CTD with Global Summit Review enabled
2.	Is the clinical section legible and organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
LABELING					
6.	Has the applicant submitted a draft prescribing information that appears to be consistent with the Physician Labeling Rule (PLR) regulations and guidances (see http://www.fda.gov/Drugs/GuidanceComplianceRegulatory Information/LawsActsandRules/ucm084159 htm	X			PLR labeling in Module 1.14.1.3
SUMMARIES					
7.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			Clinical efficacy and safety summaries are submitted
8.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
9.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
10.	Has the applicant submitted a benefit-risk analysis for the product?	X			Found in Clinical Overview in Module 2.5
11.	Indicate if the Application is a 505(b)(1) or a 505(b)(2).				505(b)(1) application
505(b)(2) Applications					
12.	If appropriate, what is the relied upon listed drug(s)?			X	
13.	Did the applicant provide a scientific bridge demonstrating the relationship between the proposed product and the listed drug(s)/published literature?			X	
14.	Describe the scientific bridge (e.g., BA/BE studies)			X	
DOSAGE					
15.	If needed, has the applicant made an appropriate attempt to determine the correct dosage regimen for this product (e.g., appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Treatment Arms:	X			The dose of LNG is intermediate between two previously approved intrauterine systems (Skyla and Mirena).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Location in submission:				
EFFICACY					
16.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 CSR A52238 (Protocol 91665/310442) Indication: Prevention of pregnancy	X			
17.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			Three-year 2-arm study (LCS 16 and Skyla) followed by a 2-year single-arm extension study
18.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
19.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	The outcome variable is pregnancy, which is measured objectively. No rationale for applicability of foreign data is needed.
SAFETY					
20.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
21.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			X	
22.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
23.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dosage (or dosage range) believed to be efficacious?	X			
24.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
25.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	X			MedDRA version 17.1 Module 1.14.1.5
26.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
27.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			Pregnancy and serious adverse reactions narratives are included
OTHER STUDIES					
28.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			X	
29.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
30.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			Pediatric waiver request in Module 1.9.1
PREGNANCY, LACTATION, AND FEMALES AND MALES OF REPRODUCTIVE POTENTIAL USE					
31.	For applications with labeling required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, has the applicant submitted a review of the available information regarding use in pregnant, lactating women, and females and males of reproductive potential (e.g., published literature, pharmacovigilance database, pregnancy registry) in Module 1 (see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307 htm)?	X			Found in Module 1.14.1.5
ABUSE LIABILITY					
32.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
33.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	Not needed for this application
DATASETS					
34.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			Statistical analysis submitted in Module 5.3.5.3
35.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
36.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
37.	Are all datasets to support the critical safety analyses available and complete?	X			
38.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
39.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
40.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
FINANCIAL DISCLOSURE					
41.	Has the applicant submitted the required Financial	X			Module 1.3.4

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

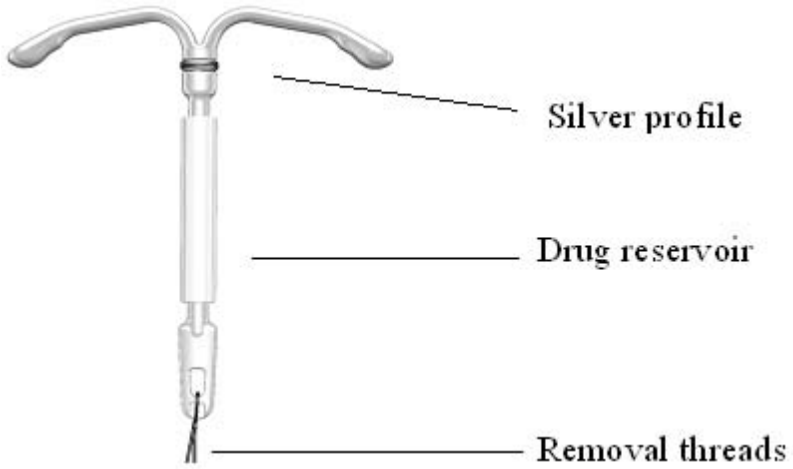
	Content Parameter	Yes	No	NA	Comment
	Disclosure information?				
GOOD CLINICAL PRACTICE					
42.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? ____Yes____

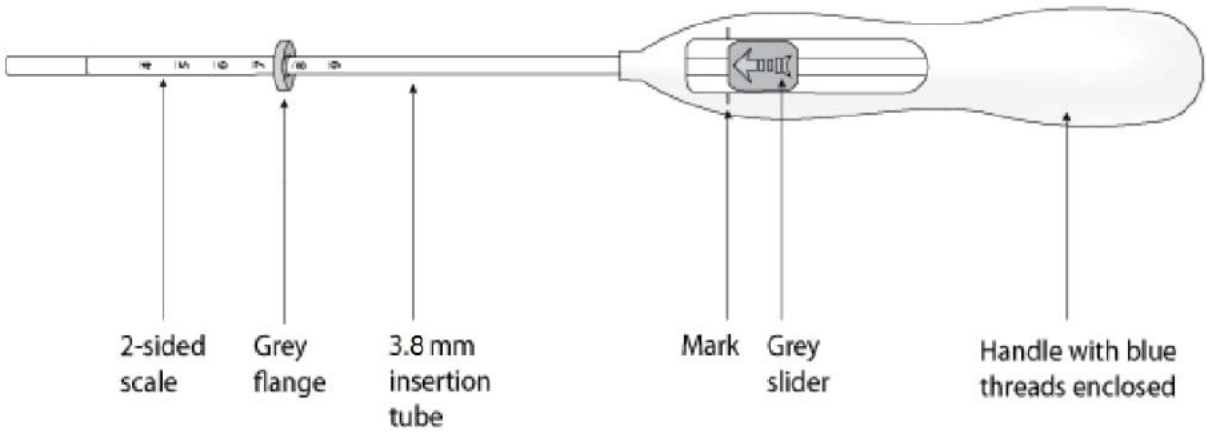
SUMMARY OF SUBMISSION

This NDA is for LCS16, which is a levonorgestrel (LNG) intrauterine system (IUS) that has been developed for use with duration of action of 5 years. Bayer is seeking an indication for prevention of pregnancy for up to 5 years, similar to Mirena.

T BODY



[redacted] INSERTER



- The LCS16 IUS consists of a hormone-elastomer reservoir mounted on a T-shaped polyethylene frame (T-body). The IUS is identical to Skyla in size with the exception of the [redacted] drug core which has been lengthened from 13 mm to 19 mm to accommodate the increase in LNG.
- The drug reservoir consists of (1) the inner stem (2) a drug core composed of 19.5 mg LNG, and (3) a covering outer membrane [redacted]
- The removal threads will be blue to differentiate from Skyla, which has brown removal threads.
- The T-body contains a silver ring in the upper part of the vertical stem to aid in ultrasound detection and to differentiate the IUS from Mirena, which has no silver ring.
- The to-be-marketed inserter will be the [redacted] inserter (threads are prefixed inside the shaft) which has been approved in the US for use with Skyla and Mirena.
- The inserter used in the phase 3 efficacy study and the phase 2 study differs from that proposed for marketing approval. The "[redacted]" Inserter that was approved for use with Skyla is proposed for marketing with the LCS12 (the inserter dimensions and operation are identical; the only difference is in color of some components of the inserter. A similar, but larger, [redacted] inserter has also been approved for Mirena. The Applicant proposes to rely upon clinical data for the [redacted] inserter obtained with Skyla to support approval of the [redacted] inserter with LCS16.
- A marketing application for LCS16 has also been submitted to the European Union.

Bayer IUS Comparisons

	NDA 208224 LCS16	NDA 203159 Skyla (LCS12) Approved 2009	NDA 21225 Mirena Approved 2000
Duration of action	5 years	3 years	5 years
LNG content	19.5 mg	13.5 mg	52 mg
Initial *in vitro* release rate	16 µg/day	12 µg/day	20 µg/day
In vivo release rate 1 year	9.8 µg/day	6.0 µg/day	18 µg/day
In vivo release rate 3 years later	7.9 µg/day	5.4 µg/day	(b) (4) µg/day
In vivo release rate 5 years later	7.4 µg/day	-	10 µg/day
Mean *In vivo* release rate over 5 years	9.0 µg/day	-	(b) (4) µg/day
(b) (4) inserter	To be marketed inserter	Approved	Approved

TWO CLINICAL STUDIES

Phase 3 Pivotal Study: CSR A52238 (Protocol 310442)

Study	Design	Study Population	Number of Women included/completed (N=2885/1689)	Main Outcomes
-IND 73,505 -138 sites -11 countries (Europe, US, Canada, South America) -2007-2011 -Extension until 2013	-Multicenter, randomized, open label, -2-arm, parallel group -3 years (up to 5 years for LCS16 only)	-Healthy women -18- to 35 years -nulliparous and parous women	-LCS12: 1432/819 -**LCS16: 1453/870** -Extension study: **-LCS16: 707/550**	-Pregnancy rate -Bleeding pattern -Safety

Phase 3 Pivotal Study CSR A52238 (Protocol 310442)

- The primary pregnancy rate is based on data from women 18 to 35 years of age. During the first year of use (Year 1 PI) and for the total treatment duration of 5 years (5-year PI) in the pivotal study A52238.
- The PI was based on pregnancies that occurred after the onset of treatment and within 7 days after IUS removal or expulsion.
- Months that included the use of back-up contraception, but in which conception did not occur, were not included in the calculation of the PI.
- From 1453 subjects in study A52238, a total of 707 women entered the 2-year extension study and 550 subjects completed the study.

Phase 2 Supportive Study: CSR A46796 (Protocol 308901)

Study	Design	Study Population	Women Included/Completed (N=741/530)	Main Outcomes
- -IND 73,505 -37 sites in 5 countries in Europe -2005-2011	-Multicenter, randomized, open label, 3-arm, -3 year trial	-Healthy women **-21 to 40 years** -nulliparous and parous women	-LCS12: n = 239/174 **-LCS16: n = 245/174** -Mirena: n = 254/182	-Pearl Index -Life table -Bleeding pattern -Safety -Pharmacokinetics

Phase 2 Supportive Study CSR A46796 (Protocol 308901)

- LCS16 was compared to Skyla and to Mirena
- Study was done entirely in Europe
- Inclusion and exclusion criteria were similar between the pivotal study A52238 and the phase 2 study. Relevant differences between the two studies are the different inclusion criteria regarding age, i.e., 18 to 35 years in study A52238 compared to 21 to 40 years in study A46796.
- LCS16 arm = 245 women
- Mean duration of treatment was 912 days (2.5 woman years)
- Pregnancies (N=6)
  - LCS12 = 1
  - LCS16 = 5 (2 ectopic; 2 spontaneous abortion; 1 carried to term)

Pooled Studies

- A total of 1,452 subjects in the phase 3 trial and 245 subjects in the phase 2 trial were enrolled. A total of 550 subjects completed 5 years of LCS16.
- For both studies, a total of 1530.42 woman-years on LCS16 for the first year (19,895 cycles)
- For both studies, a total of 2821.07 woman-years on LCS16 at the end of 2 years (36,673.91 cycles)
- For both studies, a total of 3918.52 woman-years on LCS16 at the end of 3 years (50,940 cycles)
- The overall cumulative exposure to LCS16 during the 5 years of LCS16 treatment was about 67,931 28-day equivalent cycles or 5225.52 woman-years

EFFICACY

The efficacy of LCS16 was demonstrated in the phase 3 clinical trial that enrolled generally healthy women aged 18–35, 1,452 of whom received LCS16.

- The clinical trial had no upper or lower weight or BMI limit.
- For LCS16-treated women, 563 (38.8%) were treated at US sites and 889 (61.2%) were at non-US sites.
- 80.2% of treated subjects were Caucasian.
- The weight range for LCS16-treated subjects was 38 to 173 kg (mean weight: 68.7 kg) and mean BMI was 25.3 kg/m^2 (range 15.2–57.6 kg/m^2).

The pregnancy rate calculated as the Pearl Index (PI) in women aged 18–35 years was the primary efficacy endpoint.

- The PI was calculated based on 28-day equivalent exposure cycles;
- Evaluable cycles excluded those in which back-up contraception was used unless a pregnancy occurred in that cycle.
- LCS16-treated women provided 16,207 evaluable 28-day cycle equivalents in the first year and 57,313 evaluable cycles over the five year treatment period.
- **The PI estimate for the first year of use based on the 2 pregnancies that occurred after the onset of treatment and within 7 days after LCS16 removal or expulsion was 0.16 with a 95% upper confidence limit of 0.58.**
- **The unadjusted 5-year cumulative failure rate for LCS16 was 1.445% (95% CI (0.823, 2.531.**

Primary Phase 3 Study, CSR A52238, Unadjusted FAS*

	LCS16			LCS12
PI's	**Women/ Pregnancies**	**WY**	**PI and Upper Bound**	**PI and Upper Bound**
Year 1	**1452/2**	**1252.43**	**0.16 (0.58)**	**0.41 (0.96)**
Year 1 PI by Age				
-18-35 years	1452/2	1252.43	0.16 (0.58)	
-18-25 years	564/1	473.19	0.21 (1.18)	0.22 (1.22)
-26-35 years	888/1	779.24	0.13 (0.72)	0.53 (1.35)
-Year 1 PI by Parity				
-Nulliparous	575/0	473.39	0.00 (0.78)	0.45 (1.62)
-Parous	878/2	779.34	0.26 (0.93)	0.39 (1.14)
Year 2	1206/4	1066.87	0.37 (0.96)	0.30 (0.86)
Year 3	1010/4	897.75	0.45 (1.14)	0.24 (0.88)
3-year PI	1452/10	3217.05	0.31 (0.57)	0.33 (0.60)
Year 4	773/1	659.17	0.15 (0.85)	N/A
Year 5	636/2	558.30	0.36 (1.29)	N/A
5-Year PI	**1452/13**	**4434.53**	**0.29 (0.50)**	
5-Year PI by Age				
-18-35 years	**1452/13**	**4434.53**	**0.29 (0.50)**	N/A
-18-25 years	564/3	1628.02	0.18 (0.54)	
-26-35 years	888/10	2806.51	0.36 (0.66)	
5-Year PI by Parity				
-Nulliparous	574/4	1636.24	0.24 (0.63)	N/A
-Parous	878/9	2798.28	0.32 (0.61)	
5-Year PI by BMI				
<30 kg/m^2	1198/1	1037.82	0.10 (0.54)	N/A
>30 kg/m^2	250/1	211.06	0.47 (2.64)	

*Individual exposure in terms of days of treatment; not 28-day cycle equivalents

SAFETY

- There was one death in study CSR A52238, a suicide in a 20 year-old woman related to problems with depression and eating disorder, assessed by the investigator as unrelated to study drug. This subject was in the LCS16 cohort.

- Safety data for supporting the (b) (4) Inserter is based on 3 studies (Protocols 13362, 13363 and 14371)

Bleeding/Spotting

- Bleeding evaluation was based on the pooled studies.
- The Division requested the 28-day reference periods

28-day Cycle Equivalent	Cycle 1 N=1,619		Cycle 4 N=1,575		Cycle 7 N=1,518		Cycle 13 Year 1 N=1,394		Cycle 39 Year 3 N=913		Cycle 65 Year 5 N=322	
Days on treatment	1–28		85–112		169–196		337–364		1065–1092		1793-1820	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Number of bleeding days	7.2	5.9	3.2	3.6	2.2	3.0	1.5	2.4	1.0	2.0	0.9	1.8
Number of spotting days	8.6	6.0	4.6	4.4	3.5	3.4	2.9	3.0	2.2	2.6	2.1	2.4

Adverse Reactions

Most common adverse reactions (occurring in ≥ 5% users) were:

- Vulvovaginitis (24.3%),
- Ovarian cyst (22.2%),
- Abdominal pain/pelvic pain (20.7%),
- Headache/migraine (15.4%),
- Acne/seborrhea (15.4%),
- Dysmenorrheal/uterine spasm (10.0%),
- Breast pain/breast discomfort (9.7%),
- Increased bleeding (7.9%).

The most common adverse reactions leading to discontinuation were:

- Increased bleeding (4.5%),
- Abdominal pain/pelvic pain (4.2%),
- Device expulsion (2.7%),
- Acne/seborrhea (2.2%),
- Dysmenorrhea/uterine spasm (1.3%).

Serious Adverse Events

In the pooled studies, serious AEs were reported in 98 (5.8%) women. These include

- A total of 10 ectopic pregnancies
- Six cases of pelvic inflammatory disease
- Two cases of uterine perforation

DISCONTINUATIONS

Of the LCS16-treated women,

- 21.6% discontinued the study treatment due to an adverse event,
- 5.0% were lost to follow up,
- 2.3% withdrew for unspecified reasons,
- 1.2% discontinued due to protocol deviation,
- 0.9% discontinued due to pregnancy,
- 19.6% discontinued due to other reasons.

RETURN OF FERTILITY

- About 71.2% of women wishing to become pregnant conceived within 12 months after removal of LCS16

REGULATORY ISSUES

The following issues were satisfactorily addressed by Bayer in the Application:

- Regarding efficacy, the phase 3 trial is the stand-alone pivotal study.
- The pivotal trial contained more than the required number (10,000) of cycles
- At least 39% of the subjects were from North America
- "During treatment" pregnancies were defined as pregnancies with estimated date of conception after the insertion of LCS16 and within 7 days after removal of LCS16 or detection of expulsion.
- The evaluation of efficacy was based on the 12 month and cumulative 5-year unadjusted Pearl Indices for women 18 to 35 years of age from the phase 3 study.
- The PIs were calculated based on completed 28-day cycle equivalents.
- These PIs were also calculated for subgroups stratified by age, parity, body mass index.
- Bayer agreed the exposure would be calculated using all completed 28-day cycles in which no back-up contraception was used. Thirteen (13) cycles would constitute 1 woman-year.
- Bayer provided the bleeding data by 28-day reference periods.
- For Skyla, if a month in which back-up contraception was used might span two or more 28 day cycles, the Applicant developed an algorithm to assign back-up to a single specific 28-day cycle equivalent in such cases. What is the plan for LCS16?
- The Applicant should provide the Division with both the to-be-marketed LCS16 IUS and the marketed Skyla IUS.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

The Application is fileable.

No review issues but convey the following comments:

- For Skyla, if a month in which back-up contraception was used might span two or more 28 day cycles, the Applicant developed an algorithm to assign back-up to a

single specific 28-day cycle equivalent in such cases. What is the plan for LCS16?

- The Applicant should provide the Division with 12 samples of both the to-be-marketed LCS16 IUS and the marketed Skyla IUS with their respective inserters.

Ronald J. Orleans, M.D.	1/15/16
Reviewing Medical Officer	Date
Lisa Soule	1/14/16
Clinical Team Leader	Date

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

/s/

RONALD J ORLEANS
01/15/2016

LISA M SOULE
01/15/2016