CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203159Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	January 9, 2013
From	Lisa M. Soule, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	203-159
Applicant	Bayer Healthcare Pharmaceuticals, Inc.
Date of Submission	December 9, 2011
PDUFA Goal Date	October 9, 2012 (extended to January 9, 2013)
Proprietary Name / Established (USAN) names	Skyla Levonorgestrel (LNG)-releasing intrauterine system (IUS)
Dosage forms / Strength	IUS containing 13.5 mg LNG, inserted into the uterine cavity, to be removed/replaced after three years
Proposed Indication(s)	Prevention of pregnancy for up to 3 years
Recommended:	***Approval***

1. Introduction

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

This application seeks approval for a smaller LNG-containing IUS that also contains a silver ring to aid in detection by ultrasound. Approval is sought for use by both parous and nulliparous women. The Applicant evaluated two IUSs in its single phase 3 trial, which are referred to as LCS12 and LCS16. The two IUSs have the same T-body dimensions, (b) (4) both are smaller than Mirena. LCS12 contains 13.5 mg LNG, has an initial daily *in vitro* release rate of 12 µg LNG and is intended to provide three years' contraception, while LCS16 contains 19.5 mg LNG, has an initial daily *in vitro* release rate of 16 µg LNG and is intended to provide five years' contraception. Approval is sought in this NDA only for LCS12, which has the proprietary name Skyla; data on LCS16 are not reviewed here.

The currently available IUSs are not specifically indicated for nulliparous women. The ParaGard label makes no mention of parity, although the requirement that the uterus sound to 6-9 cm might exclude some nulliparous patients. The Mirena label states in the Indications and Use section that "Mirena is recommended for women who have had at least one child." Insertion instructions also recommend that the uterus sound to a depth of 6-10 cm. The origin of the parity recommendation in the Mirena label is not entirely clear; the original 2000 review notes that one of the registration studies required women to have been pregnant at least once, although nulliparae were allowed, while another study of 200 women enrolled solely nulliparous women. The reviewer stated that "Since pelvic infections and infertility have been historically associated with some IUDs, and since infertility is a serious issue for a nulliparous woman, it is prudent to avoid using the levonorgestrel IUD in nulliparous

women, at least until data accrues to give some assurance that fertility is not impaired…in general, it should not be used as a first choice of contraception in this group."

Nonetheless, professional associations such as the American College of Obstetricians and Gynecologists have encouraged use of IUSs and other long-acting reversible contraceptive methods as first-line contraception options in sexually active teenagers[1], without reference to parity. The CDC's Medical Eligibility Criteria for Contraceptive Use[2] categorizes the LNG IUD (Mirena) as category 2 (benefits typically outweigh risks) for women younger than 20 years of age, with a comment that concern exists about the risk of expulsion in nulliparae. Therefore, there appears to be a need for a hormonal IUS that is indicated in women without respect to parity, and by extension, in younger women. In addition, the size of this LCS IUS and diameter of the insertion tube may facilitate successful insertion in nulliparous women and thereby potentially increase acceptability Skyla in this population.

2. Background

2.1 DESCRIPTION OF PRODUCT

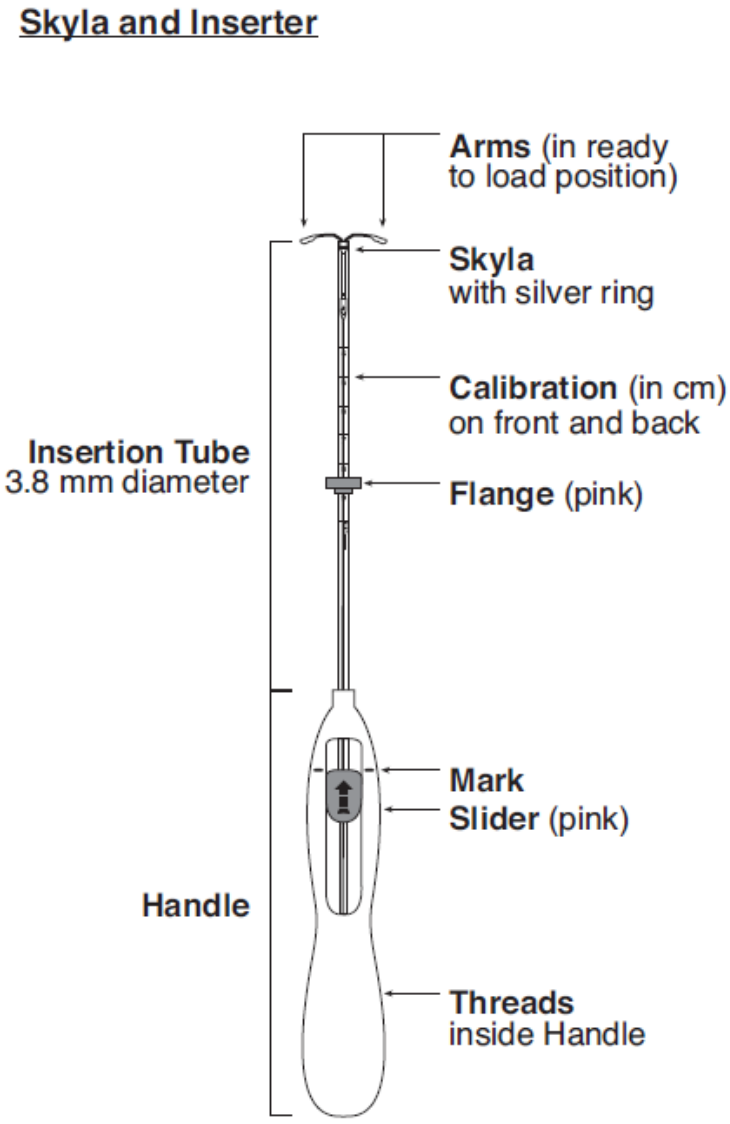
LCS12 is a drug delivery system that is regulated as a medicinal product with device components forming an integral part of the system. The IUS comprises a hormone-elastomer reservoir that is mounted on a polyethylene T-frame. The drug reservoir is composed of a drug core matrix and a polydimethylsiloxane membrane (b) (4) Compared to Mirena, LCS12 has a lower daily release rate and a smaller size, for both the T-frame and the insertion tube diameter. (b) (4) A silver ring has been added around the vertical stem of the T-frame, to facilitate detection on ultrasound and to differentiate the LCS12 from Mirena on imaging.

The IUS is introduced into the uterus via a preloaded inserter. (b) (4) This modified (b) (4) inserter has been used in additional clinical trials that were ongoing at the time of NDA submission and will be used commercially. The polyethylene removal threads were also changed (b) (4) but continued to meet specifications for breaking force. The IUS and inserter are shown in Figure 1.

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

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

Figure 1 Graphic of LCS12 and Inserter



LNG is a commonly used progestin in combination hormonal contraceptives (CHCs). It is the active pharmaceutical ingredient in the approved IUS Mirena, which has an initial daily *in vitro* release rate of 20 µg LNG. The Applicant has developed two smaller IUSs, LCS12, with a daily *in vitro* release rate of 12 µg LNG and LCS16, which has a daily *in vitro* release rate of 16 µg LNG. The smaller IUSs were developed to provide intrauterine contraception for women with smaller uterine cavities (i.e., nulliparous women) and for women who may desire child-bearing sooner than five years.

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

cervix and effects at the uterus and fallopian tubes also inhibit sperm mobility and function, impeding fertilization.

2.2 REGULATORY HISTORY

The Applicant conducted the drug development program for this indication under IND 73,505. The Division provided preIND advice in preliminary meeting comments in April 2006, after which the Applicant cancelled the meeting. At this time, the Division requested that the proposed phase 3 trial include a minimum of 10,000 28-day cycles in the first year of use, with 45% of this data in North American subjects. The Applicant initially proposed to (b) (4) Because the formulation used in the phase 2 study differed from that to be used in phase 3, the Division indicated that it would consider the phase 3 data as the primary support of the indication. Additional comments were provided by Clinical Pharmacology regarding the bridging of the phase 2 and phase 3 products, and regarding the planned development of an *in vivo/in vitro* correlation (IVIVC) model. No additional nonclinical studies were requested beyond those already conducted with the PDMS (b) (4) membrane and the chronic tolerance study of a modified version of the IUS in monkeys.

The IND was opened in July, 2007 with a protocol for the phase 3 study intended to evaluate two doses (LCS12 and LCS16) in women without regard to parity, body weight or body mass index (BMI). Clinical comments were conveyed after a protocol amendment submitted in 2009; these comments included a recommendation to stratify the safety and efficacy results by parity, to perform routine pregnancy testing at 12- and 24 month visits, and to collect data about use of back-up contraception.

An End-of-Phase 2 meeting was held in November 2009, which focused on results from the three-year phase 2 study, modifications to the development plan, development of the IVIVC and bridging the two formulations. The Applicant now proposed to extend the evaluation of the LCS16 to five years; the Division agreed with the stipulations that annual pregnancy testing be done in the extension phase and that at least 200 women complete the full duration of treatment for which approval was sought. The Applicant had not implemented planned formulation changes in the phase 3 product (actual changes consisted only of adding the silver ring and other minor modifications due to manufacturing optimization) and proposed to forego a demonstration of bioequivalence. The Division noted that if the phase 3 trial provided efficacy and safety data sufficient to support approval, bridging to the phase 2 product would not be necessary. The Division requested that the short-term *in vitro* release rate profile be characterized by including sufficient sampling time points, including as early as Day 1 or Day 2.

A CMC meeting was held in February 2011, at which sampling times for the *in vitro* release rate method were agreed upon. Dissolution and release rate specifications were also discussed.

The preNDA meeting was held on July 28, 2011. There were no outstanding CMC or nonclinical issues other than a reminder that final study reports for all nonclinical studies conducted to support the application should be submitted. Development of the IVIVC model was discussed further. The Applicant stated that the LCS12 mechanism of action appears to

be entirely local, with no evidence of ovulation inhibition, and proposed to exclude any pregnancies occurring after LCS removal as "on-treatment" pregnancies. The Division requested inclusion of any pregnancies conceived within the window of removal plus 7 days to account for variability in dating. It was agreed that efficacy evaluation would rely mainly on the 12-month and cumulative three-year Pearl Indices in women aged 18-35 years in the phase 3 trial. Because very few women over age 35 were enrolled, a Pearl Index in this older group would not be computed. The Division asked that exposure time be expressed as 28-day cycles beginning from insertion and that cycles in which back-up contraception was used be nonevaluable; however, the Applicant noted that data on back-up contraception was collected monthly, not in 28-day cycle intervals because the Applicant had planned to calculate the Pearl Index based on women-years of exposure. The Division asked that the Pearl Index calculations be submitted based on both exposure periods, and that the Applicant develop an algorithm to attribute back-up to a specific 28-day cycle in cases in which the month in which such use occurred spanned two 28-day cycles. No details were collected about what type of back-up contraception was used, but the protocol specified only barrier methods. The Applicant noted that only about 4% of subjects used any back-up.

The Division recommended that the bleeding profile data should include women of all ages and be based on 28-day cycle equivalents. The Applicant suggested that the NDA would qualify for priority review based on use in a new population (nulliparous women); the Division disagreed, stating that Mirena is not specifically contraindicated in nulliparae and, in fact, is recommended in clinical practice guidelines and widely used in this population.

Subsequent to this meeting, the proprietary name Skyla received conditional acceptance. The Applicant provided information on how it would utilize 28-day cycles in the efficacy and bleeding analyses, and the Division indicated its concurrence with the plan. The Division also agreed that bleeding would not be characterized as "scheduled" or "unscheduled."

During this review cycle, the Applicant was asked to submit additional data on the (b) (4) inserter being utilized in several phase 3b studies; these data were provided on August 10, 2012. Because this was about 60 days prior to the original PDUFA date, the submission was classified as a major amendment, and the PDUFA clock was extended by 90 days, to January 9, 2013. These data on the to-be-marketed inserter are discussed in Section 8.8.2.

A marketing authorization for LCS12 was sought simultaneously in Europe, with the Swedish health authority acting as the Reference Member State. Approvability concerns noted by this body relate to risk of ectopic pregnancy in nulliparous women and are further discussed in Section 8.8.1. Approval was granted with labeling pertaining to use by nulliparous women on December 4, 2012.

2.3 PRIMARY MEDICAL REVIEWER'S RECOMMENDATION FOR APPROVABILITY

The primary reviewer, Dr. Ron Orleans, stated in his review dated December 24, 2012:

> *Based on the data submitted in Bayer HealthCare Pharmaceutical's (the Applicant's) NDA submission, I recommend that NDA 203159 be approved for the indication of prevention of pregnancy for up to 3 years. This recommendation is*

based on the Applicant having demonstrated an acceptable Pearl Index (PI) and an acceptable safety profile for this product.

Team Leader Comment:
I concur with Dr. Orleans' recommendation.

Dr. Orleans did not recommend any postmarketing risk evaluation and mitigation strategies or postmarketing studies.

3. CMC/Device

3.1 CMC

Information about the drug substance was cross-referenced to a DMF, which determined to be adequate in August 2011. The drug product is very similar to that approved under NDA 21-225. An expiry of 24 months was granted based on adequate stability data.

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

Sites involved in manufacturing, testing and packaging were evaluated by the Office of Compliance and an "Acceptable" recommendation was made on January 7, 2013.

However, deficiencies were identified as follows:

- Functionality of the modified inserter not fully accepted by CDRH reviewer
- Pending labeling negotiations
- Pending preapproval inspection of inserter manufacturing site

The primary Chemistry Reviewer, Tarun Mehta, Ph.D., made the following recommendations in his review dated August 6, 2012:

*This applicant of this submission has **not** submitted sufficient information to assure the identity, strength, purity and quality of the drug product.*

*The Office of Compliance has **not** made an overall "Acceptable" recommendation for the facilities involved in this submission.*

*Also, the issues on label/labels are **not** resolved satisfactorily as of this review date.*

*Therefore, from the ONDQA perspective, this submission is **not** recommended for approval in its present form per 21 CFR 314.125(b)(1), (6) and (13).*

Subsequently, the Applicant submitted satisfactory revised process control parameters and excipients specifications and acceptable labeling, and the Biopharmaceutics and CDRH reviewers made "approval" recommendations. Following resolution of these issues, Dr. Mehta provided an addendum to his review dated January 7, 2012, in which he concluded:

*This NDA is **now** recommended for **Approval** from the ONDQA perspective.*

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

Additional review was done by ONDQA Biopharmaceutics staff regarding changes made to the to-be-marketed formulation compared to the phase 3 formulation, which required *in vitro* dissolution data to support bridging of the formulations.

3.2 Biopharmaceutics

The ONDQA Biopharmaceutics reviewer, Sandra Suarez Sharp Ph.D., reviewed the acceptability of the Applicant's *in vitro* drug release rate method, the acceptability of the drug release rate specifications, and the dissolution data and f2 test to bridge the change in formulations. The drug release rate method and acceptance criteria were agreed-upon, and the long-term dissolution profile comparisons indicated that the clinical trial and to-be-marketed formulations have similar in vitro drug release ($f2 > 50$). She also reviewed the Applicant's proposed *in vivo/in vitro* correlation (IVIVC) model developed by a modified Level A approach, but determined that the model failed to predict the LNG *in vivo* release for the first three months post-insertion. For this reason, the model would be acceptable only to waive the bioequivalence (BE) requirement for three months to three years. An *in vivo* BE study of exposure during the first three months would be required to support future manufacturing changes. (b) (4)

Dr. Suarez Sharp made the following recommendation in her review dated November 26, 2012:

> *The ONDQA/Biopharmaceutics team has reviewed original NDA 203-159 submitted on Dec 9, 2011, and its amendments subsequently submitted.*
>
> *The following drug release method and acceptance criteria have been already agreed upon with the Applicant (refer to submission dated Sep 27, 2012):*

Dosage Form	Apparatus	Speed	Medium	Volume (mL)	Sampling times	Acceptance criteria
IUR	Bottle/ rotary water-bath (b) (4) Shaker	70 strokes Per min	1.0% 2-ydroxypropyl-β-cyclodextrin (2-HPBCD) dissolution medium at 37 °C.	75 mL	Days 2, 11, and 25	(b) (4) Meets USP <724> L1, L2 or L3 criteria as appropriate

> *The setting of the acceptance criteria was based on the in vitro performance of the batches tested in the phase 3 clinical trial.*
>
> *From the Biopharmaceutics perspective, NDA 203-159 for Low dose levonorgestrel-releasing intrauterine system, 13.5 mg is recommended for approval.*

4. Nonclinical Pharmacology/Toxicology

No new nonclinical studies of LNG were conducted or submitted by the Applicant. Acute toxicity, mutagenicity and tolerability studies were conducted on the components of the LCS12, as was a nine-month chronic toxicity study in monkeys using a size-modified LCS12. The components of the inserter were well-tolerated and did not show cytotoxic or skin sensitization potential. Similarly, assessment of the silver ring on the T-body and the LCS12 itself in the monkey study showed no local tolerance or safety concerns. While silver does have cytotoxic potential, calculations showed that the daily release from the LCS12 is at least 3000-fold lower than the EPA established oral reference dose for silver (daily human exposure likely to be without appreciable risk of harmful effects during a lifetime).

The primary Toxicology Reviewer, Kim Hatfield, Ph.D., made the following recommendations in her review dated November 23, 2012:

> *Recommendations on approvability: Nonclinical data support approval of LCS12, levonorgestrel intrauterine delivery system 13.5 mg, for the prevention of pregnancy for up to 3 years.*
>
> *Recommendations for nonclinical studies: No additional nonclinical studies are recommended.*

Dr. Hatfield provided specific labeling recommendations that were conveyed to the Applicant.

5. Clinical Pharmacology/Biopharmaceutics

The Applicant submitted seven study reports pertaining to clinical pharmacology, but no specific clinical pharmacology study was conducted for LCS12. The pharmacokinetic (PK) and pharmacodynamic (PD) characteristics of LCS12 were based on evaluations done in the phase 2 and phase 3 studies. PK data were obtained from dense sampling of a subset of 12 women in both studies and by a population PK analysis using a sparse sampling in the phase 3 study. PD data were explored in a subset of 20 women/arm in both studies, and included effects of LCS12 on ovulation, cervical function and the endometrium, and serum silver concentrations. Other supportive data included a physiologic-based PK (PBPK) analysis that compared the PK of LNG between adolescents aged 10-18 years and adults, and two *in vitro* studies of LNG protein-binding and CYP450 enzymes involved in LNG metabolism, respectively. Two other studies were relevant to other formulations or dosing regimens and were not reviewed in this cycle.

The *in vivo* release rate of LNG was determined based on *ex vivo* residual content data obtained in phase 3, and is about 14 µg/day after 24 days *in situ*, decreasing to 10 µg/day after 60 days, and then to 5 µg/day after three years. The maximum serum concentration is attained about two days after insertion. Due to mainly local effects of LNG, intrinsic and extrinsic factors like renal/hepatic impairment and drug-drug interactions are not expected to impact efficacy or safety of LCS12. Although there were differences in LNG clearance by body weight, this is not expected to impact the safety or efficacy. The PBPK study found minimal differences in PK parameters between girls aged 15 to 18 years, with greater differences (higher PK values for younger girls) between girls aged 10 to 15 years. The median increase in Cmax and AUC for a 10 year old compared to a 30 year old was about 60%. The inclusion of the silver ring did not result in increased systemic silver exposure; concentrations measured in 24 subjects at baseline and Years 1 and 3 remained below the lower limit of quantification (1 µg/L).

> **Team Leader Comment**
>
> **The PD data were used to evaluate cervical function (scores for mucus, spinnbarkeit, ferning and cervical appearance) and ovarian function (estradiol and progesterone levels), and are discussed in Section 7.4.5.**

The primary Clinical Pharmacology Reviewer, Li Li, Ph.D., stated the following in her review dated December 5, 2012:

> *The Office of Clinical Pharmacology/Division of Clinical Pharmacology 3 (OCP/DCP3) finds NDA 203159 acceptable provided that agreement is reached between the Sponsor and the Division regarding the language in the package insert.*

Following submission of acceptable labeling, Dr. Li submitted an amendment to her review dated January 7, 2013, in which she concluded that:

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

6. Consultative Reviews

6.1 Clinical Microbiology

A clinical microbiology consult was requested for this product, and the (b) (4) sterilization process with ethylene oxide gas was reviewed. The reviewer, Jessica Cole, Ph.D., made the following recommendation in her review dated March 26, 2012:

> *This application is recommended for approval on the basis of product quality microbiology.*

No phase 4 commitments were recommended.

6.2 Center for Devices and Radiologic Health

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

- Functionality of the inserter – reviewed by Veronica Price, Biomedical Engineer
- Information pertaining to MRI labeling, because of the silver included in the IUS – two CDRH reviewers evaluated testing and labeling related to MR-induced force, torque and artifact, and radiofrequency (RF) heating
- CDRH Office of Compliance inspection – a consult was requested on May 2, 2012 to evaluate adequacy of the device manufacturing process and determine if a device-specific inspection would be required. Based on initial review, inspection of the site responsible for the final LCS12 system, Schering Oy, was assigned on September 18, 2012, to address
    - Monitoring and control of critical parameters (b) (4)
    - Compliance with appropriate regulations pertaining to design controls, purchasing controls, acceptance activities, medical device reports, complaint handling, corrective and preventive actions and corrections and removals
    - Quality systems (out of specification results/deviations/rejections) and evaluation of process data
    - Quality control data and qualification of raw material suppliers
    - Distribution supply chain

<u>Functionality of the Inserter</u>

Information on the manufacturing of the inserter was provided in a Drug Master File (DMF). Due to differences between the inserter used in phase 2 and phase 3 and that to-be-marketed,

which Dr. Price believed might impact the successful delivery of the IUS, she recommended that the DMF-holder should provide step by step details of the action of the inserter and bench testing to document successful delivery. She recommended that the Applicant provide new testing to address biocompatibility of the inserter, given that changes were made (b) (4)

The CDRH reviewer, Veronica Price, Biomedical Engineer, provided the following conclusion in her initial review dated May 16, 2012:

> *The information provided for the inserter for the Skyla system is not sufficient. Additional information is necessary to appropriately characterize the design of the inserter and to demonstrate acceptable performance ... I have included comments related to the inserter which were not directly within the requested scope of this review. These comments are included for further consideration by the CDER review team. I will leave it up to the team to decide whether it is appropriate to forward them to Bayer.*

Ms. Price provided comments about inserter function and final assembly tests that were conveyed to the DMF-holder and comments about bench testing and establishment of a shelf life for the inserter that were conveyed to the Applicant on June 15, 2012. The Applicant responded on July 6, 2012. Further comments regarding biocompatibility testing and units used to express sterilant residual levels were considered by the CMC reviewer.

Dr. Price reviewed the submitted information and concluded in her final review dated October 18, 2012 that

> *The information provided is sufficient to demonstrate adequate performance of the inserter proposed for commercial use and the maintenance of stability over a 2 year shelf life.*

MRI Testing and Labeling

The LCS12 was determined to be "MRI-conditional." Terry Woods, Ph.D., addressed testing for force, torque and artifact, and her questions and labeling comments were conveyed to the Applicant. Following discussion, acceptable labeling with respect to MRI safety and compatibility was submitted by the Applicant on January 3, 2013, and it was agreed that information about MRI scanning with the LCS in place would be conveyed to patients via the patient booklet, patient counseling section of the package insert and the patient labeling.

Wolfgang Kainz reviewed the RF heating test and found the testing acceptably done. He provided labeling comments which the Applicant accepted.

Inspection

An additional consult request was submitted to the CDRH Office of Compliance to evaluate the adequacy of the device manufacturing process for assembly of the T-body drug product into the device inserter. The reviewer, Shirley Zeigler, recommended inspection of the site responsible for production of the finished IUS and had the following conclusion in her review dated June 13, 2012:

> *CDRH recommends that the approval of NDA 203159 is deferred until the time when satisfactory preapproval inspection has been conducted at the site mentioned above.*

Inspection of the site Bayer Oy in Finland was completed on October 2, 2012. While there were no quality systems violations, one concern was identified: flaws were detected in the (b) (4) although acceptance criteria were failed for only one of three runs.

A root cause was identified and preventive maintenance instituted, but only one additional qualification run was performed. CDRH made the following recommendation after reviewing the inspection report:

CDRH has reclassified the inspection NAI [no action indicated], based on the EIR dated September 24, 2012 to October 2, 2012, because there were no supportable violations of 21 CFR part 820.

CDRH recommends follow-up with the firm t provide updated data for process qualification runs of multiple batches (b) (4) *for the Skyla product (LCS12).*

CDRH leaves to CDER, the lead Center for this inspection, to initiate any follow up actions to the violations found during the inspection and make a final decision on the overall classification of the inspection.

7. Clinical/Statistical - Efficacy

7.1 OVERVIEW OF CLINICAL PROGRAM

The clinical development program for the LCS12 included two open-label, randomized studies. Study A46796 (Protocol 308901) was a three-year phase 2 study to evaluate LCS12 and LCS16 compared to Mirena in nulliparous and parous women; this study was conducted in Europe (Finland, Hungary, Norway, Sweden and UK). Study A52238 (Protocol 310442) also evaluated the safety and efficacy of LCS12 and LCS16, and was conducted in the US, Canada, Europe and South America. This study was conducted over three years, and there was an extension phase of the LCS16 arm out to five years. Because the phase 2 study had no US component, the Division stipulated that the efficacy evaluation would be based on the phase 3 data. In addition, the formulation used in phase 2 was slightly different, (b) (4) the addition of the silver ring, and slight modification of the T-body. Because of these differences, the efficacy data reviewed here will be limited to that from the phase 3 study; however, the safety evaluation will rely upon pooled data from both studies.

An overview of the two studies is provided in Table 1.

Table 1 Clinical Studies for LCS12

Study Number Phase (No. of Sites / Country) Dates of Study Conduct	Subject Population	Primary Endpoints	Treatments	R (FAS)*	Design
A52238 **Phase 3** (138 total; 68 Non-US (56/EU, 12/ Latin Amer.); 57/US, 13/Canada Aug. 2007 to June 2011	Women 18 to 35 years of age, nulliparous or parous	Pearl Index	LCS12	1432 (1432)	2-arm, randomized, open-label, multicenter, multinational parallel group, 3-year with 2-year extension for LCS16
			LCS16	1453 (1452)	
			Total	**2,885 (2,884)**	
A46796 **Phase 2** 37 (EU) April 2005 to Dec. 2008	Women 21 to 40 years of age, nulliparous or parous	Pearl Index	LCS12	241 (240)	3-arm, randomized, open-label, multicenter, multinational parallel group, 3-year
			LCS16	245 (245)	
			Mirena	258 (256)	
			Total	744 (741)	

*R = Randomized Subjects, FAS= Full Analysis Set
Source: Based on Table 1-1, Clinical Overview, NDA 203-159, p 9

7.1.1 Study A52238

Study A52238 was a prospective, multicenter, randomized, open-label, two-arm trial, and was the sole phase 3 trial in the Applicant's clinical development program. The objective of the trial was to evaluate LCS12 and LCS16 in nulliparous and parous women aged 18 to 35 years. While the study was open because the two LCSs have obvious differences in the (b) (4) subjects were not told which LCS they received until the first three years of treatment were complete.

Notable entry criteria included regular menstrual cycles (21 to 35 days); "suitable general and uterine conditions" for insertion; more than six weeks postpartum, with fully involuted uterus. Women were excluded for a history of ectopic pregnancy, uterine infection within three months before screening; current or history of pelvic inflammatory disease (PID); uterine anomaly or distorted uterine cavity (e.g., by fibroids); clinically significant ovarian cyst(s); established immunodeficiency, known or suspected HIV infection or at high risk for sexually transmitted infections(STIs); or uncontrolled hypertension (>140/90 mm Hg).

LCS insertion was performed no more than seven days after the onset of menses, or at the time another contraceptive method was discontinued. Subjects were withdrawn after two failed insertion attempts or following complete or partial expulsion of the LCS, perforation, PID, or a persistent ovarian cyst > 5 cm for three months. Missing two consecutive scheduled visits without a major reason was also grounds for withdrawal. The Applicant also established a plan to stop recruitment if an unacceptable pregnancy rate was observed at any

point for either arm. In non-US sites, placement was verified by a transvaginal ultrasound (TVU) following insertion; this was not done at US sites because this is not consistent with standard of care in clinical practice following IUS insertion. Women were instructed to use condoms for contraception starting at least seven days prior to LCS removal (unless the removal took place during early menses).

Study A52238 enrolled 2,885 women; this study was conducted in North America (the US [57 sites], Canada [13 sites] and Mexico [4 sites]), Europe (Finland [15 sites], France [8 sites], Hungary [8 sites], Netherlands [9 sites] Norway [5 sites], Sweden [11 sites]) and South America (Argentina [5 sites] and Chile [3 sites]).

7.2 DEMOGRAPHICS

Demographics were similar in the two arms of the study. The mean age was about 27 years, and the mean weight about 69 kg (~152 lbs. The mean BMI was 25.3 kg/m^2, with a range (not shown) of 15-58 kg/m^2. About 80% of the subjects were Caucasian, with 5% Black, 11% Hispanic, 1% Asian and 3% "other." About 39% of women in each arm were nulliparous.

Table 2 shows the demographics of the modified Full Analysis Set (FAS) population in Study A52238, which is defined as all randomized subjects who received at least an attempted insertion.

Team Leader Comments

- **The proportion of Caucasians is higher than that in the general US population, but race/ethnicity is not expected to impact the safety or efficacy of the LCS.**
- **The study included a reasonably high proportion of nulliparae, which should be sufficient to allow evaluation of safety and efficacy in this subgroup.**

Table 2 Study A52238 – Demographics and Baseline Characteristics – FAS Population

Variable	LCS12 N = 1432 (100%)	LCS16 N = 1452 (100%)	Total N = 2884 (100%)
Mean age (years [range])	27.2 [18-35]	27.1 [18-35]	27.1 [18-35]
Ethnic group (n [%])			
Caucasian	1142 (79.7%)	1164 (80.2%)	2306 (80.0%)
Mean weight (kg)	68.7	68.7	68.7
Mean height (m)	1.647	1.647	1.647
Mean body mass index (kg/m^2)	25.32	25.32	25.32
Parity: nulliparous	556 (38.8%)	574 (39.5%)	1130 (39.2%)
Currently sexually active	1416 (98.9%)	1435 (98.8%)	2851 (98.9%)
Current smokers	334 (23.3%)	360 (24.8%)	694 (24.1%)
Mean number of cigarettes smoked per day	7.8	7.9	7.9
Alcohol consumption: seldom/occasional	1067 (74.5%)	1079 (74.3%)	2146 (74.4%)
Education level: some secondary	970 (96.3%)	996 (96.7%)	1966 (96.5%)

N = total number of women

Source: Based on Study Report for A52238, Table 8-8, page 76

7.3 DISPOSITION OF SUBJECTS

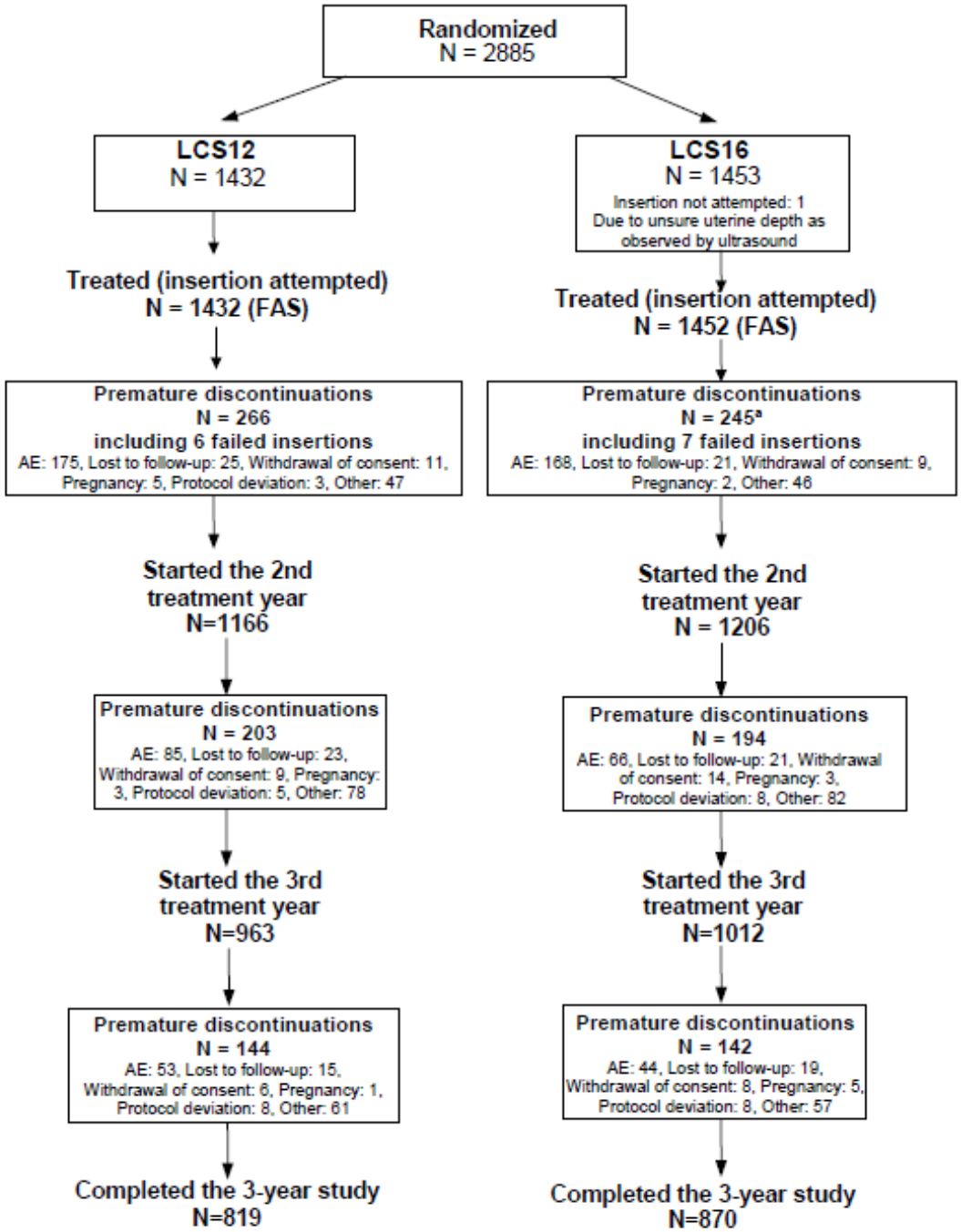
A total of 3,661 women were screened for the study, with 2,885 randomized. Of these, 2,884 women had at least one attempted LCS insertion, with 1,432 receiving the LCS12. This constituted the FAS population. Of the total sample size, 1,103 (38%) were enrolled in the US and 184 (6%) in Canada. Of these, a total of 805 received the LCS12.

The disposition of subjects over the initial three years of the study is displayed in Figure 2. Reasons for premature discontinuation are provided in Table 3.

Team Leader Comments

- **North American (excluding Mexico) women comprised almost half of the study population.**
- **The proportion of withdrawals each year was similar across LCS arms (Year 1: 18.6% and 16.9%; Year 2: 17.4% and 16.1%; Year 3: 15.0% and 14.0%, for LCS12 and LCS16, respectively). Reasons for premature discontinuation were also very similar across treatment arms.**
- **Reasons included in the "other" category for women with the LCS12 were predominantly desire for pregnancy (62%), and moving (18%). Less common reasons in this category included no further need for contraception, partner felt strings, accidental removal and failed insertion.**

Figure 2 Subject Disposition, First Three Years



a One additional subject (Subject 150147 [LCS16]) should have been documented as 'prematurely discontinued' and not as 'study medication never administered', since insertion was attempted and the subject is included in the FAS.

Source: Study Report for A52238, Figure 8-1, page 70

Table 3 Number and Reasons for Premature Discontinuation

No of subjects	LCS12 N = 1432 (100%)	LCS16 N = 1453 (100%)	Total N = 2885 (100%)
Study medication never administered [a]	0	2 (0.1%)	2 (<0.1%)
Completed first 3 years	819 (57.2%)	870 (59.9%)	1689 (58.5%)
Prematurely discontinued	612 (42.7%)	581 (40.0%)	1193 (41.4%)
Missing	1 (<0.1%)	0	1 (<0.1%)
Reason for discontinuation			
n	**613 (100.0%)**	**583 (100.0%)**	**1196 (100.0%)**
Withdrawal of consent	26 (4.2%)	31 (5.3%)	57 (4.8%)
Protocol deviation	16 (2.6%)	16 (2.7%)	32 (2.7%)
Adverse event	313 (51.1%)	278 (47.7%)	591 (49.4%)
Lost to follow-up	63 (10.3%)	61 (10.5%)	124 (10.4%)
Pregnancy	9 (1.5%)	10 (1.7%)	19 (1.6%)
Other b	186 (30.3%)	186 (31.9%)	372 (31.1%)

[a] Formally, Subject 150147 (LCS16) should have been documented as 'prematurely discontinued' and not as 'study medication never administered', since insertion was attempted and the subject is included in the FAS.

Source: Study Report for A52238, Table 8-2, page 71

The Applicant explored study discontinuations by parity. For the LCS12 arm, 28% of nulliparous women discontinued prematurely due to withdrawal of consent or an adverse event (AE), while 21% of parous women discontinued for one of these reasons. Withdrawals due to progestin-related effects, problems with bleeding or non-bleeding and "other" reasons were slightly higher among nulliparae.

Team Leader Comments

The reasons for higher rates of discontinuation among nulliparous women do not suggest a safety concern, as they primarily relate to tolerability issues such as changes in menstrual bleeding, and to the desire for pregnancy.

7.4 EFFICACY FINDINGS

7.4.1 Assessment of Efficacy in Study 302

Routine pregnancy testing was not done in the study except during the end of treatment visit, but subjects were instructed to inform the study site immediately if they became pregnant or suspected pregnancy. Subjects were provided with home pregnancy tests to use as needed. Pregnancies conceived within three months after LCS removal were to be reported. Subjects recorded use of back-up contraception on a monthly basis in the subject diary, based on a question "*Contraceptive method was used: Yes or No*." No details were collected about what type of back-up contraception was used, but the protocol allowed only barrier methods (e.g., condoms to prevent STIs). Other concomitant medication use was recorded during clinical visits (every three months for the first year, then every six months thereafter).

The Division asked that exposure time be expressed as 28-day cycles beginning from insertion and that cycles in which back-up contraception was used be nonevaluable; however, the Applicant had collected these data monthly, planning to calculate the Pearl Index based on women-years of exposure. Based on the Division's request, Pearl Index calculations were provided based on both exposure periods, and the Applicant developed an algorithm to attribute back-up to a specific 28-day cycle in cases in which the month in which such use

occurred spanned two 28-day cycles. The week prior to removal was also excluded from evaluable exposure because subjects used condoms for contraception during that week.

Team Leader Comment

In addition to relying on diary information, the Applicant also defined use of back-up contraception based WHO-based drug-code datasets to identify hormonal preparations that could be used as back-up contraception. The FDA statistical reviewer was able to create a similar dataset based on hormonal medications identified in the concomitant medications dataset. Because the results were so similar using either dataset, the FDA statistician's subsequent analyses relied upon the Applicant-provided datasets.

7.4.2 Primary Efficacy Analysis

The primary endpoint was the Pearl Index, calculated as X/E, where X = number of pregnancies, and E = exposure time, expressed in 100 women-years (WY; one WY = 365 days of IUS exposure). The Division also requested that the Applicant calculate the PI based on 28-day exposure data, in accord with the usual calculation used for hormonal contraceptives:

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

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

The analysis population was the Full Analysis Set (FAS) population, defined as all subjects who had an IUS insertion or insertion attempt. Subjects were analyzed according to the actual IUS inserted (i.e., not as intent-to-treat for those few subjects who received an IUS other than the one to which they were randomized). This population was further defined as those subjects who were between the ages of 18-35 years, with exclusion of any cycles in which an alternate method of birth control was used. Information on use of back-up contraception in each calendar month was collected in the daily diaries; missing information was imputed as no use of back-up contraception.

Team Leader Comments:

- **The population used by the Applicant is the appropriate one for evaluation of the primary endpoint (Pearl Index), and cycles in which other contraception (including condoms) was used were appropriately excluded.**
- **While the imputation of missing data as no use of back-up contraception is not ideal, the FDA statistical reviewer indicated that only 111 women in the LCS12 arm had any missing data in the first year of treatment, and the number decreased successively in subsequent years. Thus, it is unlikely that this imputation had a major impact on the number of evaluable cycles.**

Pregnancies conceived on treatment, or within 7 days after expulsion or removal of the IUS, were included in calculation of the Pearl Index, as were pregnancies that occurred after partial expulsion. The Applicant calculated Pearl Indices for Year 1, 2 and 3 individually, and cumulative Two-Year and Three-Year rates. The unadjusted Pearl Index presented here includes all exposure through removal or total expulsion of the LCS.

Team Leader Comments

- **The Division had requested that all pregnancies conceived within 7 days after removal of the LCS be counted, to allow for inaccuracy in ultrasound dating of**

pregnancy. The Applicant's documentation was inconsistent as to whether they excluded pregnancies conceived after removal vs. after removal + 7 days. According to the FDA statistician, the Applicant's analyses appear to have incorporated the 7-day window. In any case, no pregnancies were conceived within 7 days after removal, so the 7-day window does not impact the Pearl Index in this study.

- **In addition, the Applicant calculated the Pearl Index on the basis of exposure time in days, while the FDA statistician used exposure time based on 28-day cycles, as is customary. This modification did not change the results of the study.**

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

7.4.3 Primary Efficacy Results

A total of 10 pregnancies occurred in subjects in Study A52238, with six occurring on-treatment in parous women and four in nulliparae; details are shown in Table 4. Three pregnancies were ectopic (two in nulliparous women), three were spontaneously aborted, one underwent an induced abortion and three resulted in healthy infants. There were no pregnancies conceived prior to insertion or within seven days after discontinuing treatment. Timing from insertion ranged from 39 to 893 days. Five of the pregnancies occurred in the first year, three in Year 2 and two in Year 3.

Table 4 Details of Pregnancies, LCS12 Arm

Study A52238			
Subject ID	**Exposure year**	**Parity**	**Outcome**
120329	Year 3	Parous	IUS **totally expelled**, pregnancy noted at time of TVU showing expulsion. **Normal pregnancy**
120419	Year 1 (8 months post-insertion)	Parous	**Ectopic**, diagnosed during surgery for suspected appendicitis, right salpingectomy
140202	Year 3	Nulliparous	Positive HCG, TVU inconclusive for implantation, LCS removed at 4 weeks GA; **spontaneous abortion** 5 days later
141008	Year 1 (39 days post-insertion)	Parous	LCS **displaced** into cervical canal, noted at pregnancy TVU; LCS removed at 5 weeks GA; **induced abortion** 2 weeks later
160743	Year 1 (73 days post-insertion)	Nulliparous	Ectopic diagnosed by TVU, **spontaneous abortion** same day; LCS removed 5 days later. LCS visualized in "right corner" of uterus, with empty left corner, indicating **bicornuate uterus**.
190636	Year 2	Parous	Pregnancy diagnosed by HCG, TVU the next day showed 13-week fetus without heart rate and placental abruption. LCS removed with difficulty the next day, and **D&C** performed.
210519	Year 2	Parous	IUS **partially expelled**, pregnancy noted at time of TVU showing expulsion. LCS removed at ~ 7 weeks GA. **Normal infant** born by C/S due to preeclampsia at 36 weeks GA.
230303	Year 2	Nulliparous	**Ectopic** pregnancy treated with "laparoscopic extirpation;" LCS removed the prior day.
245003	Year 1 (9 months post-insertion)	Parous	Pregnancy diagnosed with home test, TVU showed LCS **displaced** into cervical canal & apparent nonviable pregnancy; LCS removed at 5 weeks; **spontaneous abortion** 11 days later
245932	Year 1 (8 months post-insertion)	Nulliparous	IUS **partially expelled** and negative HCG noted, pregnancy diagnosed 18 days later, with TVU showing displacement into cervical canal. LCS removed at ~ 7 weeks GA; **normal infant** born at term by C/S.
240364*	Year 1 (6 months post-insertion)	Parous	**Total expulsion** noted, absence of LCS confirmed by TVU & HCG negative 12 days later (November 2008). According to the OSI inspection report, at the three-month follow-up call in February 2009, subject reported a pregnancy termination in January 2009, but a complete investigation was not conducted to determine whether the pregnancy was conceived prior to expulsion. Follow-up efforts were limited to a request for medical records that were never received.
244119*	Year 1 (8 months post-insertion)	Parous	Subject discontinued after 8 months due to post-coital bleeding; HCG negative and TVU showed correct positioning prior to removal of LCS. During a three-month follow-up call, the subject reported a positive home pregnancy test, but information about date of pregnancy test, date of conception, LMP date or EDC was not obtained. Subsequent attempts to contact this subject were unsuccessful.

*** Pregnancy NOT counted in computing the Pearl Index**
Source: Study Report for A52238, Table 14.2.1/5, page 260 and Narratives, Section 16

Team Leader Comments

- **Of the 10 pregnancies, five were associated with total or partial expulsions (including "cervical displacement"). A sixth pregnancy occurred in a woman with a bicornuate uterus. Thus, only four pregnancies occurred in the face of normal placement within the uterus.**

- **Although follow-up information on Subjects 240364 and 244119 was insufficient, I do not believe either is likely to represent an on-treatment pregnancy.**

Pearl Index

The statistical reviewer, Xin Fang, Ph.D., reviewed the Applicant's data and recalculated the Pearl Index (see Table 5), using exposure based on 28-day cycles. His calculations gives a Pearl Index of 0.41 (upper bound of the 95% confidence interval [CI] is 0.96) in the first year of use. The Pearl Index (95% CI upper bound) based on 28-day cycles was 0.30 (0.86) and 0.25 (0.90) in Year 2 and Year 3, respectively. The Applicant noted that only about 4% of subjects used any back-up.

Table 5 Pearl Index Calculation, Pregnancies in Woman aged 18-35 Years, First Year of Use

Analysis	N	Total exposure	Back-up contraception exposure	Relevant exposure	Number of pregnancies	PI	95% CI
By Day[a]	1432	467280	22791	444489	5	0.411	(0.133, 0.958)
By Cycle[b]	1398	16519	756	15763	5	0.412	(0.134, 0.962)

a Reviewer's analysis based on exposure days found in the analysis dataset EXPOSUA
b Reviewer's analysis based on 28-day cycles found in the analysis dataset EFFCYC

Source: Table 6, Statistical review by Xin Fang, Ph.D., dated December 4, 2012

Kaplan-Meier Analysis

The Applicant provided cumulative Kaplan-Meier estimates of the pregnancy rate over successive years of the study based on total days of exposure, while the FDA statistician provided the same estimates based on 28-day cycles. Pearl Index calculations were also made (see Table 6), but Dr. Fang prefers the use of Kaplan-Meier estimates after the first year because they take account of when in the course of the study a pregnancy occurred. For the Kaplan-Meier analysis, Dr. Fang did not exclude cycles in which back-up contraception was used, as this would have resulted in censoring a subject and discounting the remainder of her exposure data subsequent to her first use of back-up contraception.

Table 6 Kaplan-Meier Estimates of Pregnancy Rates – Women 18-35 Years

Cumulative Time Through	Cycle Analysis[b] N=1398 women		Day Analysis[a] N=1432 women	
	Kaplan-Meier Estimate Per 100 Women	PI Definition Estimate	Kaplan-Meier Estimate Per 100 Women	PI Definition Estimate
End of Year 1	0.39 (0.16, 0.94)	0.412 (0.134, 0.962)	0.40 (0.17, 0.97)	0.411 (0.133, 0.958)
End of Year 2	0.67 (0.33, 1.34)	0.359 (0.155, 0.708)	0.68 (0.34, 1.37)	0.358 (0.155, 0.706)
End of Year 3	0.89 (0.48, 1.66)	0.330 (0.158, 0.607)	0.90 (0.48, 1.69)	0.327 (0.157, 0.601)

a. Reviewer's analysis based on exposure days found in the analysis dataset EXPOSUA
b. Reviewer's analysis based on 28-day cycles found in the analysis dataset EFFCYC

Source: Table 7, Statistical review by Xin Fang, Ph.D., dated December 4, 2012

Team Leader Comment

After Year 1, the Pearl Index and Kaplan-Meier estimates begin to diverge due to differences in calculating the exposure cohort. Based on Dr. Fang's recommendation, the labeled cumulative three-year pregnancy rate should reflect the Kaplan-Meier estimate.

Dr. Fang calculated pregnancy rates with the exclusion of the two terminated sites (2415 and 2434). The Year 1 Pearl Index was 0.42 with an upper bound of 0.98. The three-year cumulative Kaplan-Meier rate was 0.90 with an upper bound of 1.68 when these sites were excluded, compared to 0.90 (1.7) when they are included.

Team Leader Comment

The pregnancy rate is not impacted either in Year 1 or overall by the exclusion of the two sites that were terminated.

Dr. Fang also looked at efficacy in subgroups by age, US/non-US, BMI and parity (see Table 7). Race was not explored because the vast majority of the population was Caucasian.

Table 7 Pearl Index and Kaplan-Meier (KM) Pregnancy Rate by Age, US/Non-US, BMI and Parity Subgroups, 28-day Cycle Analysis*

	Year 1						3-Year Cumulative
Subgroup	**Total cycles of exposure**	**Back-up contraception exposure**	**Relevant exposure**	**Number of pregnancies**	**PI**	**95% CI**	**KM rate (95% CI upper bound)**
Age							
age ≤ 25	6,327	438	5,889	1	0.22	(0.01, 1.23)	0.97 (2.6)
25 < age ≤ 35	10,192	318	9,874	4	0.53	(0.14, 1.35)	0.85 (1.9)
US/Non-US							
US	5,904	316	5,588	2	0.47	(0.06, 1.68)	0.47 (1.9)
Non-US	10,615	440	10,175	3	0.38	(0.08, 1.12)	1.1 (2.2)
BMI							
< 30 kg/m^2	13,667	605	13,062	4	0.40	(0.11, 1.02)	0.97 (1.9)
≥ 30 kg/m^2	2,839	150	2,689	1	0.48	(0.01, 2.69)	0.47 (3.3)
Parity							
nulliparous	6,304	522	5,782	2	0.45	(0.05, 1.62)	0.94 (2.5)
parous	10,215	234	9,981	3	0.39	(0.08, 1.14)	0.86 (1.9)

* Reviewer's analysis based on 28-day cycles found in the analysis dataset EFFCYC
Source: Tables 12-15, Statistical review by Xin Fang, Ph.D., dated December 4, 2012

Team Leader Comments

- **The Division had requested at least 10,000 cycles of exposure in the first year of use, of which 45% should be in US subjects. Although the percentage specified was not met, the Applicant did provide more than 4,500 evaluable cycles in US women. This is acceptable.**
- **Confidence intervals overlapped across strata in each subgroup analysis.**
- **There is no suggestion that younger or heavier users have a higher risk of on-treatment pregnancy.**
- **Unlike typical trends seen when reviewing contraceptive data from US and non-US (European and Canadian) populations, the Pearl Index in the US population is not higher than that in the non-US subjects. This is likely because factors that may be relevant to efficacy differences for other forms of hormonal contraception (greater**

weight and BMI in American women and improved compliance in non-US women) are not pertinent to this compliance-independent, locally-acting contraceptive.

- **Nulliparous women have a slightly higher pregnancy rate but well within the confidence interval for parous women.**
- **The overall Pearl Index, as well as that for the subgroup of US subjects, provides evidence of acceptable contraceptive efficacy for a three-year duration of treatment.**

Statistician's Conclusion

Dr. Fang confirmed the Applicant's overall primary efficacy findings, using a 28-day cycle-based calculation. He verified the Applicant's exclusion of cycles in which back-up contraception was used by creating an analysis dataset that excluded cycles in which "other birth control drugs or condoms" or specific hormonal contraceptive components identified in the concomitant dataset were used. Dr. Fang noted that the Applicant calculated the Pearl Index based on exposure time in days, whereas the Division bases it on 28-day cycles; however, results were almost identical either way.

Dr. Fang made the following conclusions and recommendations regarding contraceptive efficacy in his review dated December 4, 2012:

> *From a statistical perspective, this single phase 3 study provides evidence demonstrating the efficacy of LCS12 (13.5 mg levonorgestrel contraceptive intrauterine system) for the prevention of pregnancy for up to 3 years in women 18 to 35 years of age. The Pearl Index at the end of the first year is 0.41 (95% CI is 0.13 to 0.96). Supportive evidence is based on the Kaplan-Meier cumulative pregnancy rate. The cumulative pregnancy rate per 100 women at the end of the first year is 0.39 (95% CI is 0.16 to 0.94) and at the end of the third year is 0.89 (95% CI is 0.48 to 1.66).*
>
> *There were no major statistical efficacy issues encountered in this review. One minor analysis issue was that the Applicant used exposure based on days to calculate the Pearl Index while the Agency uses exposure based on 28-day cycles. Analyses using exposure based on 28-day cycles were calculated for this review. The Pearl Index results based on either days or 28-day cycles were consistently similar.*

7.4.4 Secondary Efficacy Analysis - Bleeding Profile

Characterization of the bleeding profile was a secondary efficacy endpoint. Subjects completed a daily calendar-like diary that recorded occurrence and intensity of bleeding or spotting. The diary was reviewed at each clinic visit (at 3- to 6-month intervals); if it were missing (or some data were missing), bleeding data was obtained by questioning. The following bleeding intensity definitions were used:

- No: no vaginal bleeding
- Spotting: less than the subject's normal menses, with no need for sanitary protection (except panty liners)
- Light: less than the subject's normal menses, but requiring use of sanitary protection
- Normal: like the subject's normal menses
- Heavy: more than the subject's normal menses

A bleeding episode was defined as the number of days of bleeding that were preceded and followed by at least two bleeding-free days; a similar definition was utilized for a spotting episode. A bleeding- (or spotting-) free interval was defined as at least two days free of bleeding or spotting, and followed by at least one bleeding/spotting day. Amenorrhea was defined as the absence of bleeding throughout the reference period being assessed.

Single missing days of bleeding reports were imputed as the maximum of the bleeding intensity recorded on the day before or day after the missing day. Consecutive days of missing data were not replaced or imputed; in this case or in the case of more than five non-consecutive days being missing in a 90-day reference period, the entire reference period was considered missing.

The Applicant initially reported bleeding data using the 90-day reference period recommended by the WHO, starting with the day of insertion. However, the Applicant also provided the first year bleeding data based on 28-day cycles, according to the Division's request. As per agreement with the Division, bleeding was not be characterized as "scheduled" or "unscheduled."

Dr. Orleans' review discusses the 90-day bleeding data; the 28-day bleeding data are presented in Table 8 and Table 9. Because the LCS insertion occurred during menses in the first month, data from Month 2 on reflects the effect of LCS12 on bleeding patterns. Subjects had a median of one bleeding episode per 28-day reference period, with a median length of 5 days in Cycle 2, decreasing to 1 day by Cycles 10-12 (means were slightly higher).

Based on 90-day reference periods, women who received LCS12 had a 3% rate of amenorrhea in the second period, 6% by the fourth (end of Year 1), 9% by end of Year 2, and 11% by end of Year 3. Rates of "infrequent bleeding" (1-2 bleeding/spotting episodes per 90-day period) remained fairly constant at about 20% throughout the three years of treatment, "frequent bleeding" (> 5 bleeding/spotting episodes per 90-day period) decreased from 12% in the second 90-day period to 4% by the end of Year 3, "irregular bleeding" (3-5 bleeding episodes and < 3 bleeding/spotting-free intervals of ≥ 14 days) decreased from 28% in the second period to 17% in the penultimate quarter of Year 3, and "prolonged bleeding" (bleeding/spotting episodes lasting > 14 days) decreased from 17% to 2% over the same interval.

Table 8 Bleeding Days per 28-Day Cycle (First 12 Cycles)

Cycle	N	Mean (SD)	Min	Median	Max
1	1357	7.5 (5.7)	0	6.0	28
2	1347	5.5 (4.8)	0	5.0	28
3	1330	4.3 (4.1)	0	4.0	28
4	1307	3.7 (3.5)	0	3.0	24
5	1290	3.3 (3.4)	0	3.0	28
6	1275	3.1 (3.3)	0	3.0	28
7	1244	2.9 (3.2)	0	2.0	24
8	1216	2.6 (2.9)	0	2.0	22
9	1208	2.4 (3.0)	0	2.0	24
10	1182	2.4 (3.0)	0	1.0	22
11	1154	2.3 (2.7)	0	1.0	18
12	1144	2.2 (2.9)	0	1.0	28

Source: Integrated Statistical Analysis of Safety and Efficacy – US, Table 176, page 1040

Table 9 Spotting Days per 28-Day Cycle (First 12 Cycles)

Cycle	N	Mean (SD)	Min	Median	Max
1	1357	9.2 (6.2)	0	8.0	28
2	1347	6.7 (5.7)	0	5.0	28
3	1330	5.6 (5.0)	0	4.0	28
4	1307	4.8 (4.4)	0	4.0	28
5	1290	4.0 (4.0)	0	3.0	28
6	1275	3.9 (3.8)	0	3.0	25
7	1244	3.9 (3.7)	0	3.0	28
8	1216	3.5 (3.4)	0	3.0	27
9	1208	3.3 (3.2)	0	3.0	21
10	1182	3.4 (3.3)	0	3.0	24
11	1154	3.3 (3.3)	0	3.0	23
12	1144	3.2 (3.2)	0	3.0	18

Source: Integrated Statistical Analysis of Safety and Efficacy – US, Table 179, page 1049

Team Leader Comments

- **Subjects consistently had more spotting than bleeding days during each cycle and the number of each decreased steadily throughout the first year of treatment.**
- **Undesirable categories, such as frequent, irregular and prolonged bleeding/spotting, also decreased throughout treatment.**
- **Rates of amenorrhea remained modest, but did increase over the course of treatment. This likely shows a dose-response effect, because the rate of amenorrhea was higher (21%) by the end of Year 3 with the LCS16, and has been reported as about 20% at the end of Year 1 for Mirena.**

7.4.5 Other Efficacy Data

Pharmacodynamic Data

PD data to assess cervical and ovarian function were collected in a subset of subjects (20 who got the LCS12 per study) twice a week for a six-week period each year of the phase 2 and phase 3 studies. The cervical score was the sum of subscores for amount of mucus,

spinnbarkeit, ferning and visual inspection of the cervix (total between 0-12). The total score averaged about 3, indicating a thickening of cervical mucus.

Ovulation was evaluated annually based on serum progesterone, using two cut-off criteria, ≥ 2.5 ng/ml, based on internal modeling, and ≥ 3 ng/ml, based on the literature. Ovulation was identified in all women in the phase 2 study at all sampling periods, and in all women except one (who did not show evidence of ovulation in Years 1 and 2) in the phase 3 study. These results did not vary according to the progesterone cut-off used.

In addition, estradiol and progesterone levels were assessed at the same time points. While there was high variability, there was no clear increase or decrease in either hormone over the years of treatment.

Team Leader Comment:

LCS12 does not inhibit ovulation; thus, the mechanism of action is likely to rely upon effects on cervical mucus, sperm motility and the endometrium.

Ease of Insertion and Removal

Insertion and removal data are reported for the pooled data from the phase 2 and phase 3 studies because the same inserter was used in both trials. Overall, 99.6% had successful insertion; for the LCS12, the first insertion was successful in 96.7% of women; of the 55 in whom it failed, 52 had a second attempt, which was successful in 92.3%. Of the 59 total failed insertions, 56% were attributable to inserter problems (inserter became unsterile 1, IUS came out immediately after insertion 16, malfunction 16), 19% to patient problems (tight cervix 4, small uterus 2, pain 3, uterine position 2), and the remaining 25% to unspecified other (15) reasons. Of failed first insertions, 53% occurred in nulliparae; rates of success by parity were 95.2% (579/608) for nulliparous women and 97.6% (1038/1064) for parous women.

Local anesthesia was used in 8% of LCS12 insertions, most often given before insertion. Analgesics were given to 34%, also most often before insertion. Nulliparous women more commonly received anesthesia or analgesia. Investigators assessed insertions as "easy" for more than 90% of LCS12 and LCS16 and for 86% of Mirena insertions; insertions were rated as "very difficult" for 1.2% of each LCS and for 1.6% of Mirena insertions. Ease of insertion was evaluated as more difficult for nulliparous women, with about 84% of LCS insertions rated "easy" compared to 75% of Mirena insertions, and approximately 2% of all IUS insertions rated as "very difficult."

Subjects' evaluation of pain during the insertion was none to mild for 66% of LCS12 and LCS16 women, and 57% of Mirena woman; pain was related as severe by 8% of LCS12, 6% of LCS16 and 7% of Mirena women. Nulliparous women generally reported higher levels of pain with insertion (for all IUSs).

Removal ease by the investigator's assessment was similar across arms, with about 90% rated as "easy." For the LCS arms, 2% were assessed as "very difficult" compared to none in the Mirena arm. Removals in the LCS16 arm were limited because over two-thirds of subjects opted to remain in the extension phase of each study for another two years. Subjects' evaluations of pain during removal varied by parity: for the LCS12, 73% of nulliparous women rated pain as none to mild, compared to 88% of parous women, with 6% and 3%, respectively, rating pain as "severe."

7.4.6 Overall Assessment of Efficacy

The contraceptive efficacy study conducted by the Applicant provides evidence of an acceptable level of efficacy for the LCS12 in the prevention of pregnancy. The PI showed no increase with successive years of treatment (0.41, 0.30, 0.25 in Years 1, 2 and 3, respectively), and the overall pregnancy rate over the three-year course of treatment by Kaplan-Meier analysis was 0.89. The bleeding profile is acceptable, and indicates that, while most women will maintain monthly menses, the prevalence of undesirable bleeding conditions, such as frequent, irregular or prolonged bleeding decreases with time.

Efficacy was very similar regardless of parity. Insertion success was slightly lower in nulliparous women, but was > 95% on first attempt even in this subgroup. Other data considered with respect to parity suggests that the discontinuation rate (particularly due to progestin-related and bleeding AEs) and ratings of pain, particularly with insertion, are higher among nulliparous women than parous women.

8. Safety

The pooled database comprises data from the phase 2 and the phase 3 study. The pooled dataset included 1,672 women in the LCS12 arm, 1,697 women in the LCS16 arm and 256 women in the Mirena arm. Exposure characterized as 28-day cycles and women-years (WY) is presented by study, treatment arm and parity in Table 10. Overall, the Applicant provided data on almost 50,000 28-day treatment cycles for LCS12, over 17,000 of which were in nulliparous women. The Division had requested 10,000 cycles of exposure in the first year of treatment, with 45% (4,500 cycles) of this to come from North America. In addition, at least 200 women were to complete the full three-year course of treatment. The Applicant met these requests, with 19,343 cycles in the first year, and 716 women who completed three-years. Almost 7,000 of the cycles in the first year and over 16,500 overall were from North American subjects.

Table 10 Exposure by Study, Treatment Arm and Parity

Study	Study A52238		Study A46796		
Arm	LCS12	LCS16	LCS12	LCS16	Mirena
28-day cycles*					
Total	41,961	43,714	7,844	7,977	8,186
Nulliparous	15,800	16,738	1,430	1,510	1,625
Parous	26,161	26,976	6,414	6,467	6,561
Women-Years					
Total	3,219	3,353	602	612	628
Nulliparous	1,212	1,284	110	116	125
Parous	2,007	2,069	492	496	503

*** Exposure was calculated by dividing Applicant's reported total # of days of treatment by 28 and therefore may vary from the # of evaluable cycles reported in the efficacy section**
Source: Based on Integrated Statistical Analysis of Safety and Efficacy – US, Tables 71 & 72, pp 535-42

In some cases, particularly where the progestin dose may be associated with the rate of adverse events (AEs), data from both the LCS12 and LCS16 arms are discussed; otherwise, the discussion is generally limited to the LCS12 subjects.

8.1 DEATHS AND SERIOUS ADVERSE EVENTS

Deaths

One death occurred in Study A52238, a suicide in Subject 210112, a 20 year old woman who received LCS16 in January 2008. She died sometime in July 2010 and was reported by friends to have had depression and an eating disorder. Adverse events reported during the course of treatment included flu and two episodes of bacterial vaginosis. The death was not considered by the investigator to be drug-related.

Team Leader Comment:
Depression can be an adverse reaction to treatment with progestins, and is reported in the Mirena label to have occurred in about 6% of subjects in Mirena clinical trials. The rate in the LCS trials was slightly lower (see Section 8.2.2). The subject in this case did not report concomitant use of any antidepressants and apparently did not provide a history of depression at screening. It is unclear whether her reported depression was of new onset after LCS insertion. I believe it is plausible to consider this a possibly drug-related death.

Serious Adverse Events

There were a total of 78 women with SAEs in the pooled database; 66 women (4.6%) in Study A52238 and 12 (5.0%) in Study A46796). Selected potential serious adverse reactions (i.e., SAEs that might possibly be related to study drug) are shown in **Error! Reference source not found.** and other notable SAEs are discussed below. Pregnancies, including ectopic pregnancies, and PID are discussed elsewhere in this review.

Table 11 Selected SAEs in Pooled Database

Preferred Term	LCS12 N = 1,672		LCS16 N = 1,697		Mirena N = 256	
	n	%	n	%	n	%
Abdominal pain	5	0.3	4	0.2	1	0.4
Ovarian cyst, ovarian cysts ruptured, ovarian cyst torsion or hemorrhagic ovarian cyst	4	0.2	4	0.2	5	2.0
Ectopic pregnancy or ruptured ectopic pregnancy	4	0.2	9	0.5	0	
PID or tubo-ovarian abscess	3	0.2	5	0.3	1	0.4
Spontaneous abortion or incomplete spontaneous abortion or blighted ovum	3	0.2	3	0.2	0	
Completed suicide, suicide attempt or depression, suicidal	1	< 0.1	1	< 0.1	0	
Depression or affective disorder	1	< 0.1	2	0.1	0	
Anaphylactic reaction or drug hypersensitivity	1	< 0.1	1	< 0.1	0	
Adhesions, abdominal or pelvic	1	< 0.1	1	< 0.1	0	
Weight increased	1	< 0.1	0		0	
Deep vein thrombosis	1	< 0.1	0		0	
Hypertension	1	< 0.1	0		0	
Cervical dysplasia or cervix carcinoma stage 0	0		1	< 0.1	1	0.4
Vaginal perforation	0		1	< 0.1	0	
Device dislocation	0		1	< 0.1	0	
Vaginal hemorrhage	0		0		1	0.4

Source: Based on Integrated Statistical Analysis of Safety and Efficacy – US, Table 224, pp 3028-34

There were several SAEs related to suicidality or depression. In the LCS12 arm, Subject 230720 entered the trial with a history of depression, and completed the study as planned. She reported episodes of worsening depression with hospitalization 71, 85 and 103 weeks after insertion and had an SAE of a medication overdose (antidepressant/anxiolytic medication) two months before completing the trial. This was not categorized by the Applicant as a suicide attempt. Also in the LCS12 arm, Subject 244422 made a suicide attempt (superficial lacerations of the wrist), which was categorized as SAEs of suicidal depression and attempted suicide, about one year after insertion. Her medical history at entry included anxiety and eating disorder, but did not mention depression. She continued in the study for another year until her LCS was totally expelled.

In the LCS16 arm, Subject 161432 had an SAE of worsened depression about 2.5 years after insertion, having entered the trial with a history of depression and panic disorder. She was hospitalized and the SAE was considered unresolved, but she continued into the extension phase. Subject 210112 is described above under Deaths. Subject 244424 had an extensive history of substance abuse, depression and bipolar disorder, and experienced multiple episodes of substance dependence and depression (both serious and non-serious) during the trial. The SAE of affective disorder, for which she was hospitalized, began about 18 months after insertion. She was withdrawn from the study after two years when she was determined to have met the exclusion criterion regarding substance dependence or other mental health issues that could impair a subject's ability to cooperate.

The cases of hypersensitivity and anaphylaxis were to amoxicillin and shellfish, respectively, and therefore, are unrelated to the LCS products.

Adhesions were reported in Subjects 200908 (LCS12) and 180117 (LCS16). Subject 200908 prematurely discontinued the study after about 22 months due to pelvic pain determined to reflect intra-abdominal adhesions. Pregnancy and PID were ruled out. The subject had a history of a neonatal hemicolectomy and subsequent adhesiolysis surgeries. Subject 180117 was treated for salpingo-oophoritis that did not meet criteria for PID about one year post-insertion; 20 months later she reported abdominal pain and underwent laparoscopy for pelvic adhesions.

Subject 230501 was reported to have an SAE of weight gain, but completed the study. She gained 5 kg after one year of treatment and 7 more kg after two years. She underwent gastric bypass surgery; it appears that the hospitalization for this was the rationale for categorizing this as an SAE.

Subject 140807 experienced a deep vein thrombosis (DVT) about six months after LCS12 insertion. She continued in the study for another two years, but then had the LCS removed after a first degree relative experienced an idiopathic DVT, because the subject was then considered to be at increased risk for DVT.

Subject 242320 had SAEs of hypertension and bilateral atypical chest pain. She had mild events of hypertension reported 4 weeks and 2 years after insertion. Antihypertensive medication was started following the second event, but the AE was reclassified as an SAE when the subject was hospitalized almost three years into the study with atypical chest pain with associated hypertension. She was treated medically; the chest pain was considered

resolved the same day, but the hypertension was considered unresolved. No etiology of the chest pain was reported. She continued in the study as planned for another month.

Subject 160978 (device dislocation) had a partial perforation of the myometrium diagnosed by TVUS, for which she discontinued prematurely 25 months after insertion of the LCS16. The LCS was removed vaginally. She had reported lower abdominal pain 38 weeks and two weeks prior to discontinuation. Subject 180521 (LCS16) had an SAE reported of vaginal perforation, but this occurred during intercourse, almost two years after LCS insertion. The LCS remained intrauterine and the subject entered the extension phase of the study.

Subject 244602 had streptococcal sepsis, but it was associated with a respiratory strep infection, and did not represent LCS-related GAS.

Team Leader Comments:

- **There may be a dose-response evident for the SAEs related to ovarian cysts; this is not unexpected given the greater suppression of ovulation noted with Mirena compared to the LCS products.**
- **I consider three of the cases to represent suicide attempts (one completed); while clear histories of depression were not noted for all subjects prior to study entry, it appears that all had some mental health issues prior to LCS insertion. However, the rate of suicide attempt among women aged 18-35 years is about 16/10,000 women[3], so the observed frequency in the LCS12 population 3/1,672 or 17.9/10,000 women) is within this range.**
- **In general, the SAEs are consistent with those to be expected for a LNG intrauterine contraceptive; those likely to represent serious adverse reactions will be labeled.**

8.2 OTHER ADVERSE EVENTS

8.2.1 AEs leading to Discontinuation

In the pooled dataset, 313 LCS12 subjects (18.7%) discontinued prematurely due to an AE; this comprised 51% of all early discontinuations. The listing by study of AEs that caused discontinuation in ≥ 0.5% of subjects in either LCS treatment arm is presented in Table 12. Discontinuations by parity are discussed in Section 7.3.

[3] Women's Health USA 2011, http://www.mchb.hrsa.gov/whusa11/hstat/hshi/pages/217mi.html, accessed January 3, 2013

Table 12 AEs leading to Premature Withdrawal, Pooled Dataset

AE leading to withdrawal	LCS12 N=1,672		LCS16 N=1,697	
	N	%	N	%
Any Event	361	21.6	337	19.9
Vaginal, genital, uterine hemorrhage, menometrorrhagia, menorrhagia, metrorrhagia or polymenorrhea	75	4.5	66	3.9
Device expulsion*	54	3.2	51	3.0
Acne or acne cystic	46	2.8	33	1.9
Abdominal or lower abdominal pain	42	2.5	28	1.6
Dysmenorrhea or uterine spasm	32	1.9	21	1.2
Pelvic pain or pelvic discomfort	30	1.8	41	2.4
Affect lability, mood altered or mood swings	14	0.8	15	0.9
Weight increased	11	0.7	21	1.2
Depression or depressed mood	10	0.6	5	0.3
Headache or migraine or tension headache	9	0.5	10	0.6
Libido decreased or loss of libido	9	0.5	10	0.6
Dyspareunia	9	0.5	9	0.5
Breast discomfort, breast pain or breast tenderness	8	0.5	5	0.3
Abdominal distension	8	0.5	4	0.2

*** includes all expulsions regardless of whether they were characterized as an AE**
Source: Based on Summary of Clinical Safety, Table 220, pp 2747-52

Team Leader Comments:

- **Rates for specific events are slightly than those reported by the Applicant because related terms that did not reach the 0.5% threshold have been included here.**
- **In addition to the excessive bleeding complaints, an additional 4 and 5 women in the LCS12 and LCS16 arms, respectively, discontinued due to menstrual disorders that included dysfunctional bleeding, menstrual disorder, and irregular bleeding.**
- **Rates of individual AEs leading to discontinuation were generally higher in the LCS12 arm than the LCS16 arm; this is unlikely to be of clinical significance.**

8.2.2 Common AEs

The most common AEs in the pooled dataset and for Study A52238 individually are reported in Table 13, based on AEs that occurred in at least 5% of subjects in one of the LCS arms. Study A52238 is reported separately because the targeted surveillance of progestin-related AEs in the phase 2 study may have impacted the reporting of events such as acne, headache, breast pain/tenderness, mood changes, nausea and weight gain, which differed between the two studies. AEs that are clearly unrelated to Skyla (such as respiratory infections) are not included here; however, the list is not limited to those the investigators determined to be drug-related.

Table 13 Selected Common Adverse Events (≥ 2%) in the Pooled Dataset and Study A52238

Preferred Term	Pooled		Study A52238	
	LCS12 (N=1,672) n (%)	LCS16 N=1,697 n (%)	LCS12 (N=1,432) n (%)	LCS16 (N=1,452) n (%)
At least one AE	1,402 (83.7)	1,466 (86.4)	1,194 (83.4)	1,246 (85.8)
Vaginitis bacterial + gardnerella + vulvovaginal candidiasis or mycotic + vulvovaginitis + vaginal infection	390 (23.3)	436 (25.7)	330 (23.0)	380 (26.2)
Ovarian cyst + hemorrhagic ovarian cyst + ruptured + torsion	220 (13.2)	341 (20.1)	201 (14.0)	331 (22.8)
Headache + migraines + cluster headache + tension headache	253 (15.1)	262 (15.4)	184 (12.8)	149 (10.3)
Abdominal pain + tenderness + lower + upper abdominal pain	215 (12.9)	214 (12.6)	176 (12.3)	173 (12.0)
Acne + acne cystic	229 (13.7)	230 (13.6)	165 (11.5)	169 (11.6)
UTI	180 (10.8)	163 (9.6)	158 (11.0)	145 (10.0)
Dysmenorrhea	144 (8.6)	127 (7.5)	130 (9.1)	108 (7.4)
Cervical dysplasia	112 (6.7)	122 (7.2)	107 (7.5)	115 (7.9)
Cervix hemorrhage uterine + DUB + genital + uterine + vaginal hemorrhage + menometrorrhagia + menorrhagia + menstrual disorder + metrorrhagia + polymenorrhea	130 (7.8)	119 (7.0)	106 (7.4)	109 (7.5)
Pelvic pain + discomfort	105 (6.3)	130 (7.7)	102 (7.1)	125 (8.6)
Nausea + vomiting	110 (6.6)	104 (6.1)	91 (6.4)	82 (5.7)
Breast pain + discomfort + tenderness	145 (8.7)	173 (10.2)	72 (5.0)	86 (5.9)
Affective disorder + completed suicide + depressed mood + depression + depression suicidal + depressive symptom + suicide attempt	75 (4.5)	61 (3.6)	59 (4.1)	54 (3.7)
Procedural pain	76 (4.5)	75 (4.4)	58 (4.1)	54 (3.7)
Weight increased + abnormal weight gain + overweight	94 (5.6)	109 (6.4)	56 (3.9)	70 (4.8)
Mood altered + affect lability + mood swings	75 (4.5)	52 (3.1)	31 (2.2)	20 (1.4)

Source: Based on Summary of Clinical Safety, Tables 2.8 and 2.9, pp 55-56 and Tables 210, pp 1142-1215

The proportion of women who reported an AE decreased over time; for the LCS12 arm, 74% of subjects had an AE in Year 1, 52% in Year 2 and 49% in Year 3.

Overall, AEs occurred more frequently in nulliparous women. AEs likely to have been drug-related that were more common in nulliparae were acne (18% vs. 11%), dysmenorrhea (16% vs. 5%), ovarian cysts (14% vs. 11%), and abdominal pain (10% vs. 6%). Cervical dysplasia was also slightly more common (8% vs. 7%).

Team Leader Comments:

- **The Applicant reported common AEs by individual preferred terms; I evaluated the overall AE listing and "bundled" related terms, which tends to pick up less common variants that would not otherwise reach the Applicant's threshold for reporting.**

- **Many of the AEs are common complaints in reproductive aged women, and in the absence of a placebo control, it is difficult to determine if they are drug-related. However, a number of them are known progestin-associated AEs (acne, breast symptoms, mood changes, nausea, headache, etc.). Ovarian cysts and bleeding AEs are like to be related to the IUS.**

8.3 SUBMISSION-SPECIFIC SAFETY ISSUES

8.3.1 Ectopic pregnancies

There were four ectopic pregnancies in the LCS12 arm (0.2%) and 9 in the LCS16 arm (0.5%); no ectopics occurred in the Mirena arm of the pooled dataset. In the LCS12 group, two each occurred in Year 1 and Year 2; none occurred in Year 3. Ectopic pregnancies were more evenly distributed over the three years of the initial study in the LCS16 arm. In the LCS12 arm, two ectopic pregnancies occurred in nulliparous subjects and two in parous women; in the LCS16 arm, five of the nine ectopics occurred in parous women.

Of total pregnancies, 33% in the LCS12 arm and 60% in the LCS16 arm were ectopic. The Applicant calculated Pearl Indices for ectopic pregnancy (Table 14) and the FDA statistician calculated Pearl Indices by parity (Table 15).

Table 14 Ectopic Pregnancy Rates per Study and Pooled Data

	LCS12		LCS16	
	Number of Ectopic Pregnancies	Pearl Index*	Number of Ectopic Pregnancies	Pearl Index*
Study A52238	3	0.10	7	0.22
Study A46796	1	0.17	2	0.33
Pooled	4	0.11	9	0.24

***PI = Pearl Index = ectopic pregnancies occurring per 100 woman-years**
Source: Summary of Clinical Safety, Table 2-27, p 84

Table 15 Ectopic Pregnancy Rates by Parity, LCS12

Time	Parity	Study A52238		Pooled Data	
		# of Pregs	Pearl Index (95% CI)	# of Pregs	Pearl Index (95% CI)
Year 1	Nulliparous	1	0.23 (0.01, 1.25)	1	0.20 (0.005, 1.14)
	Parous	1	0.13 (0.003, 0.73)	1	0.11 (0.003, 0.59)
		# of Pregs	Kaplan-Meier estimate per 100 women (95% CI)	# of Pregs	Kaplan-Meier estimate per 100 women (95% CI)
Cumulative 3-year	Nulliparous	2	0.43 (0.11, 1.74)	2	0.40 (0.10, 1.60)
	Parous	1	0.13 (0.02, 0.93)	2	0.23 (0.06, 0.92)

Source: Based on Table 18, Statistical review by Xin Fang, Ph.D., dated December 4, 2012

Outcomes of the ectopic pregnancies in the LCS12 arm were one spontaneous abortion, two salpingectomies and one laparoscopic removal of the ectopic pregnancy. The single ruptured ectopic pregnancy occurred in the LCS16 arm.

Team Leader Comments:

- **As noted in Section 7.4.3, one LCS12 subject who had an ectopic pregnancy had a bicornuate uterus.**
- **The risk of ectopic pregnancy with IUDs has been well-characterized; while IUDs prevent both intrauterine and ectopic pregnancy, the proportion of pregnancies that are**

ectopic is likely to be higher among women using an IUD. However, as shown by the Pearl Indices, the absolute risk of ectopic pregnancy is quite low.

- **The Kaplan-Meier estimates for the ectopic rates reported by Dr. Fang are higher because they are cumulative and account for the decreasing pool of women at risk. Although the risk in nulliparous women appears to be higher than in parous women, the confidence intervals around the point estimates for each parity group overlap, and it is not possible to determine if there is a true difference. Overall, the risk of ectopic pregnancy is low regardless of parity, not exceeding 0.5%.**

8.3.2 Pelvic inflammatory disease (PID) and uterine infections

PID was diagnosed based on criteria that included tenderness on pelvic examination, current lower abdominal pain and at least two of:

- Purulent or abnormal vaginal discharge
- Increased C-reactive protein (>30 mg/L)
- Increased temperature (>38° C)
- Typical findings at laparoscopy (if other clinical evidence is controversial)
- Evidence of Chlamydia or gonorrhea in the cervical canal

However, the investigator's clinical assessment was the final decision, so not all cases in Study A52238 met these criteria. Women diagnosed with PID were withdrawn from the study and the LCS removed.

In Study A52238, there were 6 cases of PID in the LCS12 arm and 7 in the LCS16 arm; four of the LCS12 women had acute salpingo-oophoritis and two had a tubo-ovarian abscess; not all were reported as SAEs. One woman was diagnosed laparoscopically (LCS12) and one treated with D&C (LCS16); the rest were treated with antibiotics and all recovered.

Two women in Study A46796, one in each of LCS16 and Mirena, had PID and both required salpingo-oophorectomy. An additional woman in the LCS12 arm had non-serious case of salpingo-oophoritis treated with antibiotics and was not discontinued from the study.

The overall rate of PID in the LCS12 arm was 6/1,672 or 0.36%. All cases occurred in parous women. Three cases occurred in Year 1 (at 2, 4 and 39 weeks post-insertion), one in Year 2 and two in Year 3.

Cases of endometritis that did not meet criteria for PID were also assessed. There were 14 cases in the LCS12 arm (0.8%), with 11 of these occurring in the first year post-insertion. Eleven of the cases were in parous women. The LCS was removed in only two women.

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

8.3.3 Perforation/embedment

The protocols required all perforations (partial and total, regardless of location) to be reported as SAEs. A single partial uterine perforation (partial embedment of the shaft in the myometrium) was reported in a woman who received the LCS16 in Study A52238; her case is briefly discussed in Section 8.1.

8.3.4 Expulsion

Total expulsion was defined as cases in which the IUS was observed in the vagina, not shown in the uterus by ultrasound, or if the woman confirmed expulsion. Perforation was to be excluded. Partial expulsion was defined as cases in which the IUS was visualized in the cervical canal on gynecologic exam or ultrasound. Partially expelled IUSs were removed, and women were discontinued from the study after partial or total expulsion. Table 16 shows the frequency of expulsion by study and study arm.

Table 16 Total and Partial Expulsions

	LCS12	LCS16	Mirena
Study A52238	53 (3.7%)	46 (3.2%)	NA
Study A46796	1 (0.4%)	5 (2.0%)	5 (2.0%)
Pooled	54 (3.2%)	51 (3.0%)	5 (2.0%)

Source: Based on Summary of Clinical Safety, Table 4-2, page 115

In the phase 2 study, all expulsions occurred in parous women, and in the phase 3 study, the cumulative probability of expulsion for both LCSs was greater in parous women (data shown in Table 17).

Table 17 Cumulative Probability (%) of Expulsion by Parity, Study A52238

Parity	LCS12		LCS16	
	Partial	Total	Partial	Total
Nulliparous	3.5	1.3	1.8	0.4
Parous	5.2	3.5	4.7	2.0

Source: Based on Summary of Clinical Safety, Table 4-3, page 116

Team Leader Comment:
Given concerns that IUD insertion in the smaller uterus of a nulliparous woman might be more prone to expulsion, it is of interest that the rate appears higher in parous women.

8.3.5 Ovarian cysts

Subjects underwent transvaginal ultrasound (TVU) at all visits between Screening and End of Study. About 12% of women in the LCS12 arm had ovarian cysts at baseline that did not preclude enrollment. Because some sites reported implausible values, or reported follicles as small cysts, the Applicant reported on-treatment findings categorized as ≤ 3 cm (likely to represent a follicle) and > 3 cm (likely to represent a true cyst). The proportion of abnormal ovarian findings with a cyst > 3 cm ranged from 0.2 – 1.1% over the course of treatment.

Ovarian cysts over 3 cm were to be reported as AEs. In the pooled dataset, 220 LCS12 women (13.2%) reported AEs of ovarian cyst, hemorrhagic ovarian cyst, ovarian cyst rupture or ovarian cyst torsion on treatment, compared to 341 (20.1%) in the LCS16 arm and 64 (25%) in the Mirena arm. Although most cysts were non-serious and resolved spontaneously, in four women in the LCS12 arm, cysts were reported as SAEs and three of these women underwent laparoscopy.

8.3.6 Pap Smears

Subjects in both studies had Pap smears at Screening and End of Study; in Study A52238 women also had annual Pap smears. Actinomyces was not detected on any on-treatment cervical smears. Abnormal epithelial cell findings were seen in 2% of women at Screening and 4% at End of Study. Because there were very few findings in Study A46796, results for Study A52238 are presented in Table 18.

Table 18 Abnormal Pap Smear Results, Study A52238

	Screening	Month 12	Month 24	Month 36/ End of Study
# with abnormal Pap smear findings (% of N)	33 2.3%	32 2.9%	62 6.7%	51 (3.9%)
ASCUS	14 (42.4)	11 (34.4)	24 (38.7)	17 (33.3)
ASC-H	0	0	0	0
LSIL	15 (45.5)	17 (53.1)	31 (50.0)	23 (45.1)
HSIL	3 (9.1)	4 (12.5)	7 (11.3)	11 (21.6)
Squamous cell Ca	0	0	0	0

Percents in parentheses represent proportion of total # with abnormal Paps; numbers may not equal total due to occasional missing results
Source: Study Report for A52238, Tables 14.3.5/27 and 14.3.5/28, pp 1128-32

Team Leader Comment:
Although the proportion of abnormal Paps with high-grade lesions appears to increase over the duration of treatment, the absolute risk is low (0.7%) at the End of Study visit. This is consistent with the background rate of HSIL in the US population[4]

8.3.7 Return to Fertility

Women who discontinued either study due to desire for pregnancy were followed at 3 months and again at 12 months if they had not become pregnant by 3 months after stopping the study. Women who completed the phase 3 study were not asked about post-treatment plans for pregnancy, and so return to fertility data is not available for this cohort. In Study A46796, 14 of 18 LCS women (77.8%) who desired pregnancy had become pregnant by the 12-month follow-up (6 of 7 in the LCS12 arm or 85.7%). Of a total of 555 women successfully followed (regardless of whether they had expressed a wish for pregnancy), 38 had become pregnant.

By the end of the review cycle, the Applicant reported that in Study A52238, 233 women (116 with LCS12) had discontinued because of a desire to become pregnant, and 210 (90%) of these had been contacted. Six of these women had gone on to use other birth control; of those at risk for pregnancy 156 (76.5%) became pregnant within one year of discontinuing LCS. The pregnancy rate in the LCS12 arm was 76 of 99 women followed (76.8%).

Team Leader Comment:
The Applicant's data collection was not optimal, as only those women who discontinued prematurely due to a desire for pregnancy were followed in Study A52238; however, the low rate of pregnancies among the total population followed in Study A46796 suggests that most women continued contracepting after completing the LCS study. Overall, the rate of pregnancy in women who expressed a wish for pregnancy was 82/106 or 77% in the LCS12 arm.

8.4 SPECIAL SAFETY STUDIES

8.4.1 Endometrial histology and ultrasound

Endometrial histology based on annual biopsies was studied in subsets of the phase 2 and 3 (31 subjects) studies. Results showed secretory endometrium and a strong progestin effect, indicating endometrial suppression at all years of treatment; results did not differ between the LCS12 and LCS16. Endometrial findings based on the TVUs were normal in over 99% of

[4] American College of Obstetricians and Gynecologists, Practice Bulletin #99: Management of abnormal cervical cytology and histology, December 2008, reaffirmed 2010

women; at the End of Study/Month 36 visit, the highest number of abnormalities (9 women in the LCS12 arm) were reported; these included fluid in the cavity, intrauterine pregnancies, myomas and polyps.

Team Leader Comment:
The greater number of findings at the final visit is likely due to pregnancies; because pregnancy was a reason for termination of enrollment, a routine visit in which pregnancy was detected thereby became and End of Study visit.

8.4.2 BMD

BMD (lumbar spine and total hip) was studied at screening and annually (or at End of Study if the woman discontinued prematurely) in a subset of about 100 women in each arm of Study A52238 only. There were no decreases in BMD noted; results are presented in Table 19.

Table 19 Bone Mineral Density, Study A52238

		No. of women (Baseline)	Mean BMD at Baseline	No. of women (EoSIMonth 36)	Mean BMDat EoSIMonth 36	Change from Baseline
Lumbar spine	LCS12	102	1.1829	80	1.2118	0.0199
	LCS16	103	1.1793	71	1.2123	0.0293
Total hip	LCS12	102	1.0404	80	1.0466	0.0107
	LCS16	102	1.0207	71	1.0353	0.0158

BMD- bone mineral density; EoS - End of Study; measurements are in g/cm2
Source: Summary of Clinical Safety, Table 4-19, page 132

Team Leader Comment:
In women of the ages included in Study A52238, BMD is expected to show minimal change to a slight increase over time. Thus, it does not appear that LCS12 has any significant impact on BMD.

8.5 LABORATORY TESTING & VITAL SIGNS

Safety laboratory evaluations were conducted at Screening and End of Study for serum chemistry, liver enzymes, hematology, urinalysis, lipid parameters and hemoglobin A1C. Most values were within normal limits at both assessments, and changes from baseline were small and generally similar across treatment groups (LCS12, LCS16 and Mirena). In the pooled dataset, 6% of women with low baseline hemoglobin normalized during treatment with LCS12, while 4% of those with normal baseline developed low hemoglobin on-treatment, indicating little overall effect on hematologic status. The only parameters that showed an increase on treatment in the proportion of women with clinically significant laboratory findings was GGT (found in 2 LCS12 women at Screening and 5 at final visit) and blood in urine (none at screening and 5 at final visit).

Blood pressure, heart rate and weight were evaluated at Screening and at Month 12, 24 and 36. No relevant changes were noted.

8.6 POSTMARKETING SAFETY FINDINGS

No postmarketing safety data are available for LCS12 because it had not been approved anywhere at the time of submission (as discussed in Section 8.8.1, the LCS12 was approved by the EMA on December 4, 2012). However, the Applicant provided information from the

Executive Summary of the Periodic Safety Update Report (PSUR) for Mirena, covering September 2009 to September 2010 and from the Annual Report covering the interval from December 2009 to December 2010. Bayer complied with requests from Health Canada and the regulatory body in Malaysia to issue healthcare provider and patient communications reminding about potential risk of uterine perforation, and requests for similar communications have been made by Belgium and New Zealand. During the PSUR interval, the cumulative number of insertions of Mirena was estimated at almost 21 million, with over 57 million WY of exposure. Several clinical trials and observational studies were ongoing, including the EURAS IUD safety surveillance study, which has enrolled over 24,000 Mirena users.

Safety issues that remain closely monitored include abnormal pregnancy outcomes, sepsis, breast cancer, androgenic effects, anaphylaxis, depression/suicidality, thrombotic and thromboembolic events and uterine perforation. The Applicant concluded that there were no new safety concerns and no information that impacts the safety, effectiveness or labeling of the product.

The Applicant also conducted a search of the literature, finding no new safety concerns.

Team Leader Comment:
The information from the Mirena NDA does not suggest any additional safety concerns relevant to Skyla.

8.7 SAFETY UPDATE

A 120-day Safety Update Report was submitted on April 5, 2012, covering the period from September 1, 2011 through January 31, 2012. The safety update included information about five ongoing LCS clinical trials, preliminary feedback related to the European submission (see Section 8.8.1) and information from the Mirena PSUR and 2011 Annual Report.

Three of the ongoing studies (Protocols 13362, 13363 and 14371) are being conducted using the modified (to-be-marketed) inserter. Protocol 310442 represents the extension phase for the LCS16 arm, and Protocol 91775 is a phase 3 study being conducted in China, Korea and Australia. An additional 3,820 WY of exposure to LCS12 were reported in the Safety Update, representing about 33% of the total exposure. No deaths were reported. SAEs considered by the Applicant to be related included a uterine perforation (LCS16), an ectopic pregnancy, and an ovarian cyst rupture. AEs occurring with frequency > 5% (excluding infections diseases unlikely to be drug-related) included abdominal pain, acne, cervical erosion, dysmenorrhea, headache, ovarian cyst, procedural pain, uterine spasm and vaginal hemorrhage.

The Applicant also provided postmarketing AE reports to NDA 21-225, as described in Section 8.6.

An amendment to this Safety Update was provided on July 17, 2012, as a result of a change in the data lock point for Mirena, which changed the reporting interval. The amended Safety Update consisted of the Mirena PSUR covering the period from September 28, 2011 to December 23, 2011. A new safety-related action was the issuance of a DHCP in Turkey, regarding the risk of uterine perforation (similar to the action previously taken by Health Canada). The PSUR presented one new fatal case report (cerebrovascular accident following insertion of a second Mirena). Issues that continue to be closely monitored include

anaphylaxis, sepsis, meningioma, idiopathic intracranial hypertension, depression/suicidality, congenital disorders and uterine perforation. Overall, the Applicant and Dr. Orleans concluded that there were no new safety concerns.

Team Leader Comment:

I concur that no new safety signals were identified in the Safety Update or amended Safety Update.

8.8 Special Issues Relative to this NDA

8.8.1 EMA Concerns about Use in Nulliparae:

The Applicant received a preliminary report from the Swedish health authority on March 2, 2012, which noted that the product is considered nonapprovable due to concerns about risk of ectopic pregnancy in nulliparae. At that point, the Applicant was perceived as targeting the product specifically toward nulliparous women. While the overall pregnancy rate was found acceptable, there was concern that the potential adverse impact of an ectopic pregnancy on future fertility might be particularly devastating to nulliparous women, and that nulliparous women might have more difficulty identifying early signs of pregnancy due to the LCS's effect to decrease menstrual bleeding. The Applicant argued that the risk of ectopic pregnancy overall in LCS users was very low, and that any cross-study comparisons to Mirena data were not warranted. In addition, the Applicant noted that with today's earlier diagnosis of ectopic pregnancy, medical management and avoidance of complications that may impair fertility are more likely outcomes.

On December 6, 2012, the Applicant notified the Division that issues had been resolved with the EMA member state and approval granted (the LCS12 is known as Jaydess in Europe) on December 4, 2012. The Summary of Product Characteristics was provided; it is generally similar to US proposed labeling, with the exception of a statement under "Special Warnings and Precautions for Use" that "Because an ectopic pregnancy may impact future fertility the benefits and risks of using Jaydess should be carefully evaluated, in particular for nulliparous women. Jaydess is not first choice for contraception in nulliparous women as clinical experience is limited."

8.8.2 (b) (4) inserter

The to-be-marketed inserter has been studied in three studies, Protocols 13362, 13363 and 14371. The Division requested updated information, particularly concerning insertion-related events, from these studies on July 24, 2012; the Applicant's response, received on August 10, 2012, formed the basis of a Major Amendment that resulted in extension of the PDUFA clock by 90 days. The Applicant noted that data from the studies had not been formally cleaned and should not be considered final. Updates were presented covering the period from the Four-Month Safety Update to July 20, 2012, and a cumulative summary of other data not provided in the safety update was provided from the study start through July 20, 2012.

Protocol 13362 began in January 2011 and is being conducted in the US, Austria, Belgium and Germany, to assess user satisfaction with LCS12 vs. Yasmin. An interim analysis was conducted after all insertions and the one-month follow-up visit had been completed. A total of 282 subjects were randomized to LCS12 and 279 had insertions. A total of 294 women-years (WY) of exposure had accrued at the time of the update. Three women discontinued

prior to insertion of the LCS (one for protocol violation, two withdrew consent). Nulliparous women constituted 77% of the study population.

Three women (1.1%) required a second attempt at insertion, all of which were successful. Reasons for the initial failure were inserter-related (IUS did not release from the tube, slider malfunctioned, strings stuck to scissors and pulled IUS out). No partial or total perforations and no partial or total expulsions were reported. A single case of endometritis was reported two weeks after insertion.

There have been no deaths in this study; six SAEs have been reported, three of which were considered treatment-related by the Applicant. The related SAEs were an ectopic pregnancy treated with laparoscopic salpingectomy, a hemorrhagic ovarian cyst and spontaneous abortion of a pregnancy of unknown location. SAEs considered unrelated were ulcerative colitis, a heel spur, and a Pap smear with "cervical cell atypical Pap IVa," which was later downgraded from a serious AE.

Protocol 13363 began in September 2011 and is being conducted in Australia, Finland, France, Norway, Sweden and the UK to evaluate discontinuation rates for LCS12 vs. an etonogestrel implant. The study enrolled 385 subjects to LCS12, of whom 381 had an insertion attempt. Nulliparous women made up 76% of the study population. A total of 189 WY of exposure had accrued at the time of the update.

Six women (1.6%) had a failed initial insertion; of these, two did not have a second attempt. Of the four who attempted a second insertion, three were successful. Reasons for failure were equally due to subject and inserter issues (pain, uterus position, unable to pass through internal os; IUS came out immediately after insertion, IUS stayed linked to inserter and came out, device failed to deploy). No partial or total perforations were reported. Three women had partial expulsions of the LCS within a month of insertion; there were no full expulsions. A single case of salpingitis was reported 3.5 months after insertion.

One death was reported during this study, in a subject with a history of "hyperthreosis" who had used LCS12 for five months at the time of death. Details are being sought by the Applicant. Five SAEs were reported, with an ectopic pregnancy that resolved spontaneously as the only one considered related. The other four SAEs were the death already noted, two cases of plastic surgery and one of cholelithiasis.

Protocol 14371 also began in September 2011 and is being conducted in Austria, Belgium, Denmark, Finland, Germany, the Netherlands, Norway and Sweden. It is intended to evaluate the safety of LCS12 in women from menarche through the age of 18, as part of the Pediatric Investigational Plan required by EMA. The study enrolled 303 subjects, 98% of whom were nulliparous. A total of 117 WY of exposure had accrued at the time of the update.

Six women (2%) had a failed insertion, all of which were successful on the second attempt. Reasons for initial failure were mainly inserter-related (IUS came out immediately after insertion, IUS descended from fundus while removing inserter, thread stuck to scissors, IUS dislocated). No partial or total perforations were reported. Three women had partial expulsions, within 1-3 months of insertion, and one woman had a total expulsion within a month. Two other potential partial expulsions are being investigated, based on ultrasound examination. Four cases of upper genital tract infection were reported (two endomyometritis,

one endometritis and one salpingo-oophoritis); occurrence ranged from 2-4 days to 4-8 months after insertion.

One death was reported in this study, a woman who was a passenger in a motor vehicle collision. Twelve SAEs were reported with four considered related (endometritis, ovarian torsion, ovarian cyst and salpingo-oophoritis). The unrelated cases included accidents and non-pelvic infections. No on-treatment pregnancies were reported.

The Applicant was asked to compare the occurrence of perforation, expulsion and upper genital tract infection between Study A52238, using the original inserter, and these three trials, using the (b) (4) inserter. There was one partial perforation in Study A52238 vs. none in the three trials; rates of partial and total expulsion were 1.9% (Study A52238) vs. 0.8% (three studies) and 1.6% (Study A52238) vs. 0.1% (three studies), respectively. The infection rate in Study A52238 was 1.4% vs. 0.6% in the three ongoing studies. For PID specifically, the rate was 0.35% in Study A52238 compared to no cases in the three studies.

Finally, the Applicant was asked to provide information about post-insertion sonograms done on some subjects in Study 13362. This was done routinely in Germany and Austria, where it is standard practice following IUS insertion, but could have been done in other countries or at the investigator's discretion. Detailed information about the IUS location was not routinely requested, but was recorded in some cases. Of the 279 subjects, 185 (66%) had a specific location documented. Data were recorded for the rates of "compliant location" results, defined as the LCS being *in situ* (fundal) or displaced (completely intrauterine but not at the fundus), and all subjects were documented as having "compliant location." All of these ultrasounds that were conducted within two days of insertion documented *in situ* placement, and of 100 ultrasounds done at other times post-insertion, only one was noted to be displaced (but intrauterine).

Team Leader Comments:

- **Although based on small numbers, the rates of insertion failures (1-2%) compare favorably with that for the original inserter used in the phase 2 and 3 studies (3.3% failed first insertions, 7.7% failed second insertions).**
- **The data from the three ongoing studies do not indicate any safety concerns with the use of the (b) (4) inserter.**

8.9 OVERALL ASSESSMENT OF SAFETY FINDINGS

The clinical safety database for LCS12 based on the phase 2 and 3 studies included 1,6,72 subjects who provided over 49,800 28-day cycles of exposure; over 17,000 of which (about one-third) were in nulliparous women. The bulk of exposure came from the phase 3 study, which evaluated the to-be-marketed LCS12 product. The Applicant provided the number of cycles the Division had requested, overall and in North American subjects.

There was a single death in the clinical trials, a suicide, which is potentially associated with treatment, given the known association of progestins and depression. However, overall, the risk of suicide attempts does not appear to be outside the background rate. SAEs occurred in about 5% of women; the most common were related to abdominal pain, ovarian cysts, ectopic pregnancies and spontaneous abortions and PID. Most common AEs that were associated with premature discontinuation (> 2%) were menstrual bleeding disorders, IUS expulsion, acne and abdominal pain. Common AEs (5%) included vaginitis, ovarian cysts, headaches, abdominal pain, acne, dysmenorrhea, cervical dysplasia, excessive and irregular

bleeding, pelvic pain, nausea/vomiting and breast pain. IUS-related AEs such as PID, ovarian cysts, perforation and expulsion of the devices occurred at rates that do not appear excessive in comparison to the approved IUS, Mirena.

The safety profile varied slightly by parity. Nulliparous women discontinued at a slightly greater rate due to AEs or consent withdrawal; specific reasons relating to progestin-related AEs, bleeding complaints were more frequent in nulliparae. AEs also occurred slightly more frequently in nulliparous women, particularly acne, dysmenorrhea, ovarian cysts and abdominal pain. The risk of ectopic pregnancy appeared somewhat higher for nulliparae at Year 1 and cumulatively over the three-year treatment but the confidence intervals around the point estimates for the two groups overlapped and the absolute risk was very low (<0.5% over three years). The few cases of PID and the majority of endometritis cases occurred in parous women.

Overall, the safety profile of the LCS12 appears acceptable to support approval for prevention of pregnancy for up to three years in women without regard to parity.

9. Advisory Committee Meeting

An Advisory Committee meeting was not requested for this application, as it represents a lower dose delivery system using a modified and smaller device compared to that of a currently marketed product.

10. Pediatrics

The Applicant requested a waiver of pediatric studies in premenarcheal females (b) (4) because the indication is not relevant to this population. The Applicant also requested a waiver of studies in postmenarcheal females (b) (4) because safety and efficacy data for this population can be extrapolated from the adult data. The Division concurred. The Pediatric Review Committee (PeRC), on August 15, 2012, agreed to a partial waiver for patients (b) (4) and to extrapolate efficacy for patients from (b) (4) years of age.

The Applicant is conducting a one-year, single-arm, multicenter study (Protocol 14371) in Europe of 300 postmenarcheal adolescents < 18 years to evaluate safety, efficacy, discontinuation and PK data in adolescents; continuation into a two-year extension will also be offered.

11. Other Relevant Regulatory Issues

The Applicant certified that it did not use any debarred investigators. The Applicant submitted financial disclosure information for the majority of investigators in Studies (b) (6) and (b) (6) and provided due diligence information for those on whom financial disclosure information was missing. Two investigators for Study (b) (6) had disclosures: (b) (6) reported having received almost $192,000 in honoraria from the Applicant (b) (6) (b) (6) enrolled (b) (6) subjects, (b) (6) reported having received about $278,000 in

honoraria from the Applicant [redacted] enrolled [redacted] subjects, [redacted].

Team Leader Comment:
Although the financial disclosures for these two investigators reveal very large payments from the Applicant, I concur with the Applicant's assessment that the potential to bias the study findings is minimal, due to the limited number of subjects enrolled at these sites (< 0.5% of the total study population for each investigator).

The Applicant provided notice to the IND on December 21, 2010 that it had excluded an investigator, [redacted] from participating in the extension phase of Study [redacted] These problems, detected during 2008 monitoring visits, included multiple protocol deviations, enrollment of ineligible subjects, inappropriate delegation of study activities and inadequacies in source data reporting that resulted in under-reporting AEs. Site personnel were retrained; however, a follow-up audit in 2010 revealed lack of corrective actions undertaken. While the Applicant barred [redacted] from the extension phase, [redacted].

In addition, the Applicant notified the Division on February 28, 2012, that another investigator, Richard Muckerman II at Site 2432, had been implicated in fraudulent behavior related to another Applicant's study. Dr. Muckerman's research facility, PPL Clinical Research, plead guilty to a federal felony relating to obstruction of a 2010 FDA inspection. At the time of the Applicant's notification, FDA was still determining whether Dr. Muckerman would be permanently disqualified from participating in future clinical trials. His site for Study A52238 enrolled six subjects, two of whom received LCS12. No pregnancies were reported at this site; both LCS12 subjects discontinued prematurely, one due to the AE of fluid retention and the other was lost to follow-up.

Team Leader Comment:
As noted in Section 7.4.3, the efficacy data were analyzed with and without subjects from these two sites and results did not differ markedly.

The Office of Scientific Investigation (OSI) inspected four sites for Study A52238. The sites were chosen based on considerations that included the number of subjects enrolled, deviations on frequency of protocol violations or adverse event reports, and, in the case of the two foreign inspections, geographic proximity. Two sites (2439 [Melvin Seid] and 2403 [Keith Aqua]) were in the US and two (1606 [Kirsi Rinne] and 1609 [Tarja Jarvi]) were in Finland.

Dr. Seid's site (2439) enrolled 59 subjects, and received a No Action Indicated (NAI) evaluation following review of all subjects' records. The study appeared to have been conducted adequately and the data appear acceptable.

Dr. Aqua's site (2403) enrolled 51 subjects, and received a classification of Voluntary Action Indicated (VAI), following review of all subjects' records. Specific concerns included enrollment of a subject with an ovarian cyst that met exclusion criteria for size, enrollment of some subjects prior to receiving all screening laboratory tests, and poor follow-up of a subject who terminated her pregnancy (Subject #240364) following IUS expulsion. Dr.

Aqua responded to the VAI notification and stated that the amended protocol allowed enrollment of women with ovarian cysts of any size provided they were not considered clinically significant. The other observations were noted to be oversights, or related to unavailable or unrecorded data. Overall, the inspector stated that the study appeared to have been conducted adequately and the data appear acceptable.

Dr. Rinne's site (1606) enrolled 38 subjects, and received a NAI evaluation, following review of 14 subjects' records. Overall, the inspector stated that the study appeared to have been conducted adequately and the data appear acceptable.

Dr. Jarvi's site (1609) enrolled 89 subjects, and received a NAI evaluation, following review of all subjects' records. Overall, the inspector stated that the study appeared to have been conducted adequately and the data appear acceptable.

Janice Pohlman, M.D., M.P.H., from OSI made the following overall assessment and general recommendations in her review dated August 10, 2012:

> *Based on the review of preliminary inspection findings for Drs. Seid, Aqua, Rinne, and Jarvi, the study data for Study A52238 (Protocol 310442) submitted by the Applicant appears reliable in support of NDA 203159.*

12. Labeling

The Applicant submitted the proposed proprietary name Skyla, which was found to be acceptable by the Division of Medication Error Prevention and Analysis (DMEPA).

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

The label was submitted in the format prescribed by the Physician Labeling Rule (PLR); labeling for the similar product, Mirena, is already in PLR format. The package insert and patient labeling were reviewed by DMEPA, the Study Endpoints and Label Development (SEALD) team, OPDP and the Division of Medical Policy Programs (DMPP) Patient Labeling Team, and their comments were conveyed to the Applicant. Labeling pertaining to safety of MRI scanning was requested and reviewed by CDRH; language was included in the package insert, patient labeling as well as in a patient booklet and patient reminder card, which are not FDA-approved labeling.

Specific issues discussed during labeling negotiations included the Applicant's proposals to use pooled phase 2/3 data for the bleeding profile described in Section 5.5 and for the Adverse Reactions Section 6.1. In order to report adverse reactions, rather than AEs, the Applicant conducted a stepwise causality assessment approach, rather than merely accepting the investigators' determinations of which AEs were likely to be drug-related. The Division agreed to these proposals. The Applicant also provided data to support a statement about return to fertility (see Section 8.3.7). Agreement on labeling was reached on January 9, 2013.

13. Recommendations/Risk Benefit Assessment

13.1 Recommended Regulatory Action

I recommend that Skyla receive an Approval action.

13.2 Risk Benefit Assessment

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

The risks associated with this LCS are those well-characterized in association with hormonal IUDs, and the safety data do not suggest that these risks are higher for this smaller and lower LNG dose LCS. Although not specifically indicated in nulliparous women, other IUDs have been used in nulliparae for some time. The safety data on the large proportion of nulliparous women (about one-third of safety cycles) enrolled in the phase 2 and 3 studies do not suggest a unique or unacceptable safety signal when Skyla is used in women without regard to parity. Safety data obtained from ongoing studies using the new (b) (4) inserter do not suggest reason for concern associated with use of this inserter in the to-be-marketed product.

13.3 Recommendation for Postmarketing Risk Management Activities

The Applicant proposes routine pharmacovigilance activities, as well as education and training programs to ensure that prescribers able to select appropriate candidates for the product, and to insert it properly. As a condition for marketing authorization, the EMA required an active surveillance Outcomes study (EURAS-LCS12), which will enroll 26,000 women in five European countries who receive LCS12, Mirena or a copper IUD in a clinical setting with three-year follow-up. The primary outcome is unintended pregnancy; additional outcomes of interest are ectopic pregnancy, PID, and insertion difficulties.

In addition, the Applicant has initiated in Europe a large prospective non-interventional cohort study (EURAS-IUD) to evaluate the risks of Mirena and copper IUDs in new users. The study is intended to provide robust estimates of the absolute risk of serious adverse events, particularly uterine perforation. The Applicant believes that the results for Mirena will be applicable to LCS12, although LCS12 will not be included in the study.

Finally, the Applicant plans a drug utilization study in two databases to characterize new users of LCS12. The study will be conducted in the THIN database in the UK, and the PHARMO database in the Netherlands. The study will target young women, and will characterize the duration of use and indication for use for LCS12 and comparators that include first-time users of copper or LNG IUDs, progestin implants, and injectable progestin-only contraceptives.

I believe the postmarketing studies the Applicant has committed to or already initiated will provide useful information, such that no further postmarketing requirements, commitments or postmarketing risk management activities are recommended.

13.4 Recommendation for other Postmarketing Study Requirements and Commitments

I do not recommend that any postmarketing studies be required, but the Division will receive and review the study reports of the studies described above, as well as the European adolescent study.

13.5 Recommended Comments to Applicant

None

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

/s/

LISA M SOULE
01/09/2013

AUDREY L GASSMAN
01/09/2013