CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208224Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	September 16, 2016
From	Lisa M. Soule, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	208-224
Applicant	Bayer Healthcare Pharmaceuticals, Inc.
Date of Submission	November 18, 2015
PDUFA Goal Date	September 16, 2016
Proprietary Name / Established (USAN) names	Kyleena Levonorgestrel (LNG)-releasing intrauterine system (IUS)
Dosage forms / Strength	IUS containing 19.5 mg LNG, inserted into the uterine cavity, to be removed/replaced after five years
Proposed Indication(s)	Prevention of pregnancy for up to 5 years
Recommended:	***Approval***

1. Introduction

There are currently four intrauterine devices or systems (IUS) approved in the US – Mirena (NDA 21-225) and Liletta (NDA 206-229), both of which contain 52 mg LNG; Skyla, which contains 13.5 mg LNG; and ParaGard (NDA 18-680), which is non-hormonal, but contains copper that 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. Skyla and Liletta are approved for three years' use for contraception, and ParaGard is approved for ten years' use for contraception.

This application seeks approval for a new 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, as both groups were represented in the clinical trial. The Applicant evaluated two IUSs in its single phase 3 trial, which are referred to as LCS12 and LCS16. LCS12 was approved in 2013 as Skyla. Approval is sought in this NDA only for LCS16, which has the proprietary name Kyleena; data on LCS12 are not reviewed here.

The two IUSs have the same T-body dimensions, but the drug reservoir length is longer in the LCS16; both are smaller than Mirena. 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.

As proposed for LCS16, Skyla is specifically indicated for use without regard to parity. 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. (b) (4)

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.

2. Background

2.1 DESCRIPTION OF PRODUCT

LCS16 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 polyethylene frame is compounded with barium sulfate to make it radiopaque. The drug reservoir is composed of a drug core matrix and a polydimethylsiloxane membrane (b) (4). Compared to Mirena, LCS16 has a lower daily release rate and a smaller size, for both the T-frame and the insertion tube diameter. LCS16 has a higher daily release compared to Skyla, but is very similar in size. It is differentiated from Skyla *in situ* by having blue removal threads, while Skyla's are brown.

There are slight differences between the phase 2 and phase 3 LCS16 versions and between the phase 3 and to-be-marketed version. (b) (4)

The IUS is introduced into the uterus via a preloaded inserter; the IUS is supplied packaged sterile within the inserter. (b) (4)

(b) (4)

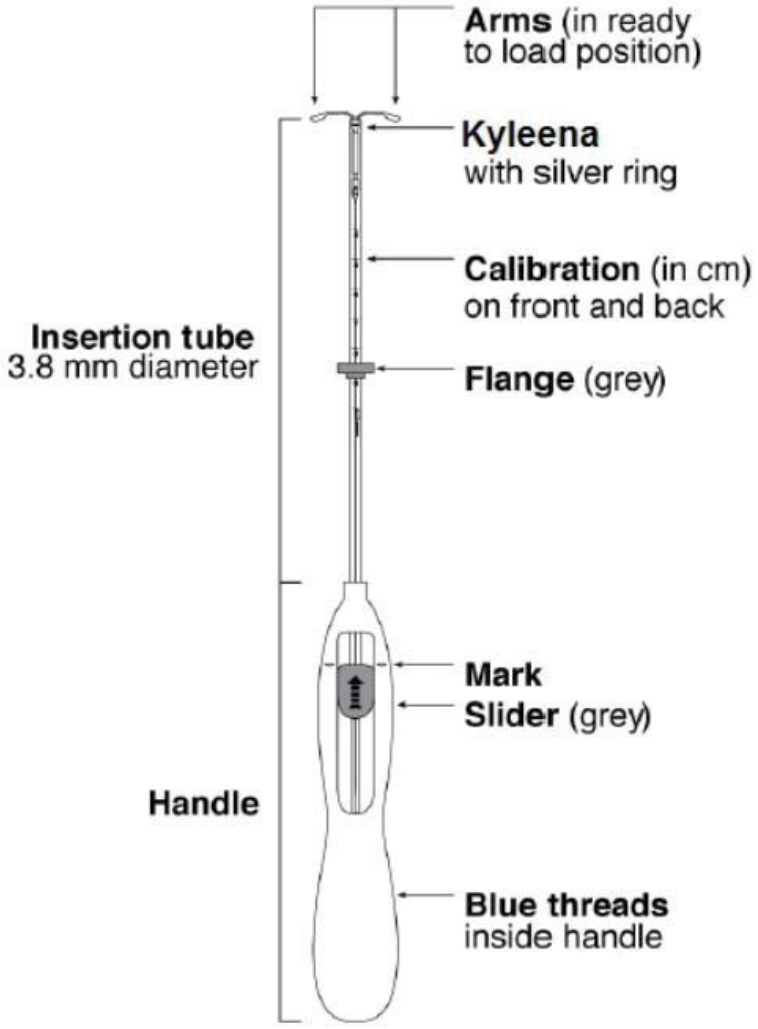
This modified (b) (4) inserter has been used in additional clinical trials, some of which were ongoing at the time of NDA submission, and will be used commercially. Evaluation of the (b) (4) inserter is discussed in more detail in Section 8.8.2. (b) (4)

The to-be-marketed 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 LCS16 and Inserter



Source: Kyleena proposed labeling

LNG is a commonly used progestin in combination hormonal contraceptives (CHCs) as well as in progestin-only emergency contraceptives and has been used in progestin-only contraceptive implants. It is the active pharmaceutical ingredient in the approved IUSs Mirena, Skyla, and Liletta. The smaller IUSs (Skyla and LCS16) 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. (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 (b) (4) 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.

A pre-NDA meeting (for the Skyla NDA) was held on July 28, 2011; while the discussion at this meeting focused on the NDA for LCS12, the same advice would apply to the subsequent application for LCS16. The Division requested inclusion of any pregnancies conceived within the window of removal plus 7 days to account for variability in dating. 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 Division also recommended that the bleeding profile data should include women of all ages and be based on 28-day cycle equivalents.

Subsequent to this meeting, 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."

A pre-NDA meeting for the LCS16 was scheduled for March 17, 2015; however, the Applicant elected to cancel the meeting after receiving the Division's preliminary comments, which included:

- Agreement that data regarding functionality of the inserter similar to that provided to support approval of a similar (b) (4) inserter for Mirena would be sufficient to support review of the (b) (4) inserter proposed for marketing with LCS16
- A request for narratives and case report forms for ALL pregnancies (including those the Applicant considered to have been conceived pre- or post-treatment); the Applicant clarified that there were no pre-treatment pregnancies, and agreed to submit a "post-treatment pregnancy form" for all pregnancies occurring more than 7 days post-treatment.
- Clarification that the primary efficacy analysis would include all pregnancies occurring on-treatment or within 7 days after LCS removal, and that the Division will rely upon the phase 3 efficacy data and not integrated phase 2/3 data to support the efficacy of the LCS
- A request for a subgroup analysis by region, US (including Canada) vs. non-US; the Applicant's proposal to categorize by North America vs. non-North America was acceptable

The proprietary name Kyleena was submitted and found to be acceptable on September 10, 2015.

A marketing authorization for LCS16 is being sought simultaneously in Europe.

2.3 PRIMARY MEDICAL REVIEWER'S RECOMMENDATION FOR APPROVABILITY

The primary reviewer, Dr. Ron Orleans, stated in his review dated September 14, 2016:

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

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

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

3. CMC/Device

3.1 CMC

The application was reviewed by members of the Office of Product Quality (OPQ) with expertise in the following areas:

- Drug substance
- Drug product
- Process
- Microbiology
- Facility
- Biopharmaceutics

The drug substance DMF was reviewed and was found to have adequate manufacturing and testing controls to assure its identity, strength, quality and purity. The drug product quality review generally found adequate in-process and release testing, and that the proposed 24-month expiration for the drug product was supported by stability data. The drug product manufacturing processes and controls were found to be adequate; (b) (4)

The overall recommendation from the OPF Division of Inspectional Assessment was "acceptable." The drug substance manufacturing and (b) (4) facilities were found acceptable based on history, as was the site that provides (b) (4) sterilization for the finished product. The drug product manufacturing site was inspected in April 2016 and found acceptable.

An inter-center 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, but has been approved for use with Skyla. The consult is discussed further in Section 6.1.

The CMC Application Technical Lead, Mark Seggel, Ph.D., made the following recommendations in his review dated August 23, 2016:

> *Bayer's 505(b)(1) New Drug Application 208224, for Kyleena (levonorgestrel-releasing intrauterine system, 19.5 mg), is recommended for Approval from the OPQ perspective.*
>
> *Kyleena (levonorgestrel-releasing intrauterine system) is regulated as a drug-device combination product. In accordance with 21 CFR 310.502(a)(8), the intrauterine system (IUS) is considered the new drug. The inserter with which the IUS is placed in the uterus is a 'device' reviewed by CDRH.*
>
> *Sufficient information and supporting data have been provided in accordance with 21 CFR 314.50 to ensure the identity, strength, quality, purity, potency and bioavailability of the IUS drug product. The drug substance and drug product manufacturing, packaging and testing facilities have acceptable CGMP status. The labeling (package insert, container/closure and secondary packaging) is complete, accurate and complies with the labeling requirements under 21 CFR 201.*

> *CDRH Office of Device Evaluation and Office of Compliance reviewers have determined that there are no deficiencies associated with the inserter device from the engineering perspective and from the medical device compliance (21 CFR 820) perspective.*

Dr. Seggel noted that the current established name for all approved LNG IUSs is "levonorgestrel-releasing intrauterine system." However, the 2014 USP Nomenclature guideline recommends "[DRUG] intrauterine system," which would translate to "levonorgestrel intrauterine system" for this product. Because there is no current USP monograph recognized under the FD&C Act for LNG IUSs, it was decided to continue the current nomenclature for all these products until such time as a USP monograph becomes official.

The OPQ review notes a commitment by the Applicant to perform stability studies on the first three production-scale batches of LCS16 in commercial packaging material up to 36 months on long-term and 6 months on accelerated storage conditions. However, Dr. Seggel indicated that this is a routine activity and does not constitute a formal Post-marketing Commitment.

3.2 Biopharmaceutics

The OPQ Biopharmaceutics reviewer, Hansong Chen, Ph.D., reviewed the acceptability of the Applicant's *in vitro* drug release method development, the discriminatory capabilities of the proposed *in vitro* release method, the *in vitro* release acceptance criteria, and comparison of long-term *in vitro, ex vivo,* and *in vivo* release rates. The proposed *in vitro* drug release method and acceptance criteria were found to be acceptable. The long-term *in vitro, ex vivo,* and *in vivo* release rates were found to be similar ($f2 > 70$). Dr. Chen did not determine any need for bridging studies between the phase 3 and the commercial product.

Dr. Chen made the following recommendation in his review dated August 4, 2016:

> *Following the above review, this Reviewer recommends that NDA 209224 for Kyleena ® (Levonorgestrel intrauterine delivery system (IUS) 19.5 mg) is* ***ADEQUATE*** *for approval from the Biopharmaceutics perspective.*

3.3 Clinical Microbiology

A clinical microbiology consult was requested for this product, and the adequacy of the container closure system to maintain product sterility and package integrity, as well as the (b) (4) sterilization process with ethylene oxide gas, were reviewed. The reviewer, Elizabeth Bearr, Ph.D., made a recommendation for approval in her review dated June 14, 2016.

No phase 4 commitments were recommended.

4. Nonclinical Pharmacology/Toxicology

No new nonclinical studies of LNG were conducted or submitted by the Applicant. Aside from the polypropylene removal thread and the polyethylene flange of the inserter, the components of the LCS16 IUS and components of the inserter that make contact with the body are identical to those for the approved Skyla IUS. Biocompatibility and genotoxicity testing in accord with ISO 10993-Part 1 and USP guidelines was done on the novel

components. Results indicate that the novel components were well-tolerated both locally and systemically, were biocompatible and were not mutagenic.

The primary Toxicology Reviewer, Alex Jordan, Ph.D., made the following recommendations in his review dated August 2, 2016:

> *Recommendations on approvability: Nonclinical data support approval of LCS16, levonorgestrel intrauterine delivery system 19.5 mg, for the prevention of pregnancy for up to 5 years.*
>
> *Recommendations for nonclinical studies: No additional nonclinical studies are recommended.*

Dr. Jordan found the labeling acceptable.

5. Clinical Pharmacology

No specific clinical pharmacology study was conducted for LCS16. The pharmacokinetic (PK) and pharmacodynamic (PD) characteristics of LCS16 were based on evaluations done in the phase 2 and phase 3 studies. PK data were obtained from dense sampling of a subset of LCS16 users (12 women planned in each of phase 2 and phase 3) and by a population PK analysis using a sparse sampling of all subjects in the phase 3 study. 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. These studies were reviewed under the Skyla NDA and were not re-reviewed.

The clinical pharmacology reviewer, Lin Zhou, Ph.D., reviewed Study Report Ph-37274 (five-year data for the phase 3 trial) and the population PK analysis report R-9266 in detail; phase 2 data had been used to develop the population PK model for LNG and were reviewed in the Skyla NDA. Data relating to elimination (metabolism and excretion) of LNG were previously reviewed under the Mirena and Skyla NDAs.

The *in vivo* release rate of LNG was determined based on *ex vivo* residual content data and plasma concentrations obtained in phase 3, and is about 17.5 µg/day after 24 days *in situ*, decreasing to 15.3 µg/day after 60 days, to 9.8 µg/day after one year, to 7.9 µg/day after three years, and then to 7.4 µg/day after five years. The average *in vivo* release rate of LNG over five years is about 9 µg/day.

The PK subset enrolled 11 LCS16 users in phase 3 and six remained at the completion of the first three years of the study. Of these, three entered the extension study and provided data through all five years. The maximum serum concentration is attained about a week after insertion and decreases slowly over the five years of use. Data based on a study with Mirena indicates that the LNG concentrations are undetectable by one week post-removal of the higher-dosed IUS.

No drug-drug interaction (DDI) or renal or hepatic impairment studies were conducted. Due to mainly local effects of LNG, intrinsic and extrinsic factors like renal/hepatic impairment and DDIs are not expected to impact efficacy or safety of LCS16. Although there were differences in LNG clearance by body weight based on the population PK analysis, with

higher LNG exposure for women of lower body weight, this is not expected to impact the safety or efficacy.

The Applicant also submitted two study reports based on Skyla (LCS12) to investigate the efficacy, safety, bleeding patterns and PK in Asian-Pacific women and in adolescents under 18 years, (b) (4).

Team Leader Comment

I concur with Dr. Zhou's conclusion that the relevance of the LCS12 data in specific populations to LCS16 has not been established, (b) (4)

PD data were explored in a subset of 20 women/arm in both studies, and included effects of LCS16 on ovulation, cervical function and the endometrium.

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.

Dr. Zhou stated the following in her review dated August 19, 2016:

> *The clinical pharmacology information in the submission is acceptable to support the approval and for inclusion in the product labeling.*

Dr. Zhou had no recommended phase 4 commitments.

Following submission of acceptable labeling, Dr. Zhou submitted an amendment to her review dated September 16, 2016, in which she concluded that:

> *The Division of Clinical Pharmacology-3, Office of Clinical Pharmacology finds the labeling for NDA 208224 acceptable.*

6. Consultative Reviews

6.1 Division of Medication Error Prevention and Analysis (DMEPA)

The DMEPA reviewer, Walter Fava, R.Ph., M.S.Ed., reviewed the risk hazard analysis submitted by the Applicant and concluded on June 10, 2016 that a Human Factors validation study was not required. Review of the proposed proprietary name is discussed in Section 12.

6.2 Center for Devices and Radiological Health

The Center for Devices and Radiological 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 Sharon Andrews, Biomedical Engineer
- Information pertaining to MRI labeling, because of the silver included in the IUS – Terry Woods, Ph.D., 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 to determine if a device-specific inspection would be required.

Functionality of the Inserter

Dr. Andrews noted that the inserter for Kyleena is identical to that approved for use with Skyla, with the exception of the gray colorant added to the slider and flange. She determined

that the colorant did not affect the biocompatibility profile because the slider is not in contact with the patient and the flange has only a short duration of patient contact. (b) (4) The IUS/inserter met acceptance criteria on breaking force minimum, recovery of horizontal arms, loading of the IUS, and detachment force. However, it was noted that the 24-month expiry accepted for the IUS (b) (4) Based on discussions with CMC, which had reviewed data supporting a 24-month expiry for the finished product (including the inserter) and on the fact that the Skyla inserter has a 24-month shelf life, Dr. Andrews concluded that it is reasonable to apply a 24-month shelf life to the Kyleena inserter.

Dr. Andrews had no labeling comments. She provided the following conclusion in her review dated September 9, 2016:

> *I have no remaining comments or deficiencies for the sponsor. The information provided is sufficient to demonstrate adequate performance of the Kyleena IUS inserter and the maintenance of stability over a two year shelf life.*

MRI Testing and Labeling

The LCS16 was determined to be "MR-conditional." Terry Woods, Ph.D., addressed testing for magnetically-induced force, torque, RF heating and artifact, which was based on testing done in 2007 for Skyla. Dr. Woods agreed with the Applicant's rationale that testing done on Skyla is applicable to the LCS16 given the identical T-body dimensions and silver ring. She found the testing acceptable, and her labeling comments were conveyed to the Applicant. Following discussion, acceptable labeling with respect to MRI safety and compatibility was submitted by the Applicant on August 4, 2016, and it was agreed that information about MRI scanning with the LCS in place would be conveyed to patients via the patient counseling section of the package insert and the patient labeling.

Dr. Woods reviewed the final submitted MR labeling and amended her review on September 12, 2016:

> *FINAL RECOMMENDATION: Approval.*
>
> *The revised labeling shown above is acceptable. I have no further questions and recommend approval.*

Inspection

An additional consult request was submitted to the CDRH Office of Compliance to evaluate the Applicant's compliance with applicable Quality System Requirements with reference to the inserter portion of Kyleena. The reviewer, Christopher Brown, determined that two facilities were subject to applicable requirements under 21 CFR part 820. Bayer Healthcare Pharmaceuticals, Inc., the Applicant, was inspected as recently as February 2016, receiving a No Action Indicated classification. A current inspection was not recommended. Bayer Oy in Finland, responsible for manufacturing, primary packaging, sterilization, secondary packaging, release and stability testing was recommended for inspection because it had not been inspected since 2012.

Further review of documents in the submission pertaining to 21 CFR part 820 regulations found areas that had not been adequately addressed relating to Management Control, 21 CFR 820.20, Purchasing Controls, 21 CFR 820.50, and Corrective and Preventive Action, 21

CFR 820.100. Following information requests regarding these deficiencies, the Applicant provided responses that were deemed adequate by CDRH.

Inspection of the site Bayer Oy in Finland was completed on April 15, 2016, and was classified as Voluntary Action Indicated due to deficiencies in six areas. There were no observations associated with the Quality System regulations.

CDRH made the following recommendation after reviewing the inspection report:

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

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

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

7. Clinical/Statistical - Efficacy

7.1 OVERVIEW OF CLINICAL PROGRAM

The clinical development program for the LCS16 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 91665310442) also evaluated the safety and efficacy of LCS12 and LCS16, and was conducted in the US, Canada, Europe and South America. This phase 3 study was conducted over three years, with an extension phase for the LCS16 arm out to five years (added with Amendment 5 to the original protocol). Results of the three-year portion were reported in Clinical Study Report (CSR) A52238, submitted as part of the Skyla NDA, while the five-year results for LCS16 were reported in CSR PH-37274. The phase 3 study will be referred to as A52238 throughout this review.

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 3 was slightly different from that in phase 2, (b) (4) 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. Details of the phase 2 study A46796 are discussed in Dr. Orleans' review. As noted, it differed from the phase 3 trial in LCS16 formulation, sample size, and geographic representation; it also had slightly different age limits for entry and provided for more frequent pregnancy testing and more targeted ascertainment of certain progestin-related adverse events (AEs).

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

Table 1 Clinical Studies for LCS16

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/Canada (56/EU, 12/ Latin Amer.); 57/US, 13/Canada Aug. 2007 to June 2011 (June 2013 for LCS16 extension phase)	Women 18 to 35 years of age, nulliparous or parous	Pearl Index	LCS12 Up to 3 years	1,432 (1,432)	2-arm, randomized, open-label, multicenter, multinational parallel group, 3-year with 2-year extension for LCS16
			LCS16 Up to 5 years	1,453 (1,452) 707 entered the 2-year extension	
			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	240 (239)	3-arm, randomized, open-label, multicenter, multinational parallel group, 3-year
			LCS16	246 (245)	
			Mirena	256 (254)	
			Total	742 (738)	

*R = Randomized Subjects, FAS= Full Analysis Set: in the phase 3 study, the FAS included all randomized women who had an insertion attempted, regardless of success; in the phase 2 study, the FAS was limited to women who had a successful insertion.

Source: Based on Summary of Clinical Efficacy, Table 1-1, p 8

In addition, data from four other studies conducted with Skyla were submitted to this NDA:

- 13362 – evaluated the (b) (4) inserter; the extension phase was ongoing at the time of NDA submission
- 13363 – evaluated the (b) (4) inserter
- 14371 – evaluated the (b) (4) inserter, provided safety data in adolescents; the extension phase was ongoing at the time of NDA submission
- 91775 – provided PK data in Asian/Pacific subjects (this study was not reviewed)

Because the studies utilized a different LCS, they are reviewed here only in the context of evaluating the (b) (4) inserter, which, despite having been used with Skyla in the three studies, has the same design and dimensions as that proposed for marketing with LCS16.

7.1.1 Phase 3 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-label because the two LCSs have obvious differences in the length of the drug reservoir, 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); uncontrolled hypertension (>140/90 mm Hg); or if they were lactating. There were no restrictions based on parity, weight or body mass index (BMI) or uterine depth.

LCS insertion was performed no more than seven days after the onset of menses, or at the time another contraceptive method was discontinued. Local anesthesia, cervical dilation and oral analgesics could be used at the inserter's discretion. 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. Placement was verified by a transvaginal ultrasound (TVU) following insertion and at subsequent study visits. 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 (data not shown). 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 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 the LCS16 arm Study A52238, which is defined as all randomized subjects who received at least an attempted insertion.

Table 2 Study A52238 – Demographics and Baseline Characteristics – LCS16 FAS Population

Characteristic	Group in 3-year Study Only N=745 n (%)	Group Continuing in 2-year Extension Phase N=707 n (%)	Overall N = 1452 n (%)
Variable category			
≤ 25 years	310 (41.6%)	254 (35.9%)	564 (38.8%)
> 25 years ≤ 35 years	435 (58.4%)	453 (64.1%)	888 (61.2%)
Age (years)			
Mean (SD)	26.6 (4.7)	27.6 (5.0)	27.1 (4.9)
Max	18, 35	18, 35	18, 35
Race			
Caucasian	581 (78.0%)	583 (82.5%)	1164 (80.2%)
Black	55 (7.4%)	19 (2.7%)	74 (5.1%)
Hispanic	81 (10.9%)	78 (11.0%)	159 (11.0%)
Asian	9 (1.2%)	8 (1.1%)	17 (1.2%)
Other	19 (2.6%)	19 (2.7%)	38 (2.6%)
Weight (kg)			
Mean (SD)	69.7 (16.2)	67.6 (14.6)	68.7 (15.5)
Min, Max	39, 173	38, 153	38, 173
Body mass index (kg/m^2)			
Mean (SD)	25.54 (5.66)	25.09 (5.30)	25.32 (5.49)
Min, Max	15.2, 56.5	15.2, 57.6	15.2, 57.6
Currently sexually active			
No	12 (1.6%)	5 (0.7%)	17 (1.2%)
Yes	733 (98.4%)	702 (99.3%)	1435 (98.8%)
Education level			
Some elementary education	7 (0.9%)	27 (3.8%)	34 (2.3%)
Some secondary education	88 (11.8%)	227 (32.1%)	315 (21.7%)
Some college or university education	285 (38.3%)	396 (56.0%)	681 (46.9%)
Information missing	365 (49.0%)	57 (8.1%)	422 (29.1%)
Previous births			
0	312 (41.9%)	262 (37.1%)	574 (39.5%)
>0	433 (58.1%)	445 (62.9%)	878 (60.5%)

BMI = body mass index; SD – standard deviation. Percentages based on N.
Source: Table 4, Statistical review by Weiya Zhang, Ph.D., dated August 19, 2016

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 LCS16.**
- **North American (excluding Mexico) women comprised almost half of the study population (US enrolled 563 women [39% of total LCS population], and Canada enrolled 92 women [6% of total LCS population] who received the LCS16).**
- **The study included a reasonably high proportion of nulliparae, which should be sufficient to allow evaluation of safety and efficacy in this subgroup.**

The Applicant was asked to address the inclusion of women who were not currently sexually active. The relevant entry criterion was that a woman be seeking

contraception, not that she be sexually active. The Applicant speculated that some women who were not sexually active at entry might be seeking contraception in anticipation of becoming sexually active, and noted that of the 17 women who reported not being sexually active at entry, 14 reported sexual activity over the course of the study, and the remaining three did not return for visits after the baseline visit.

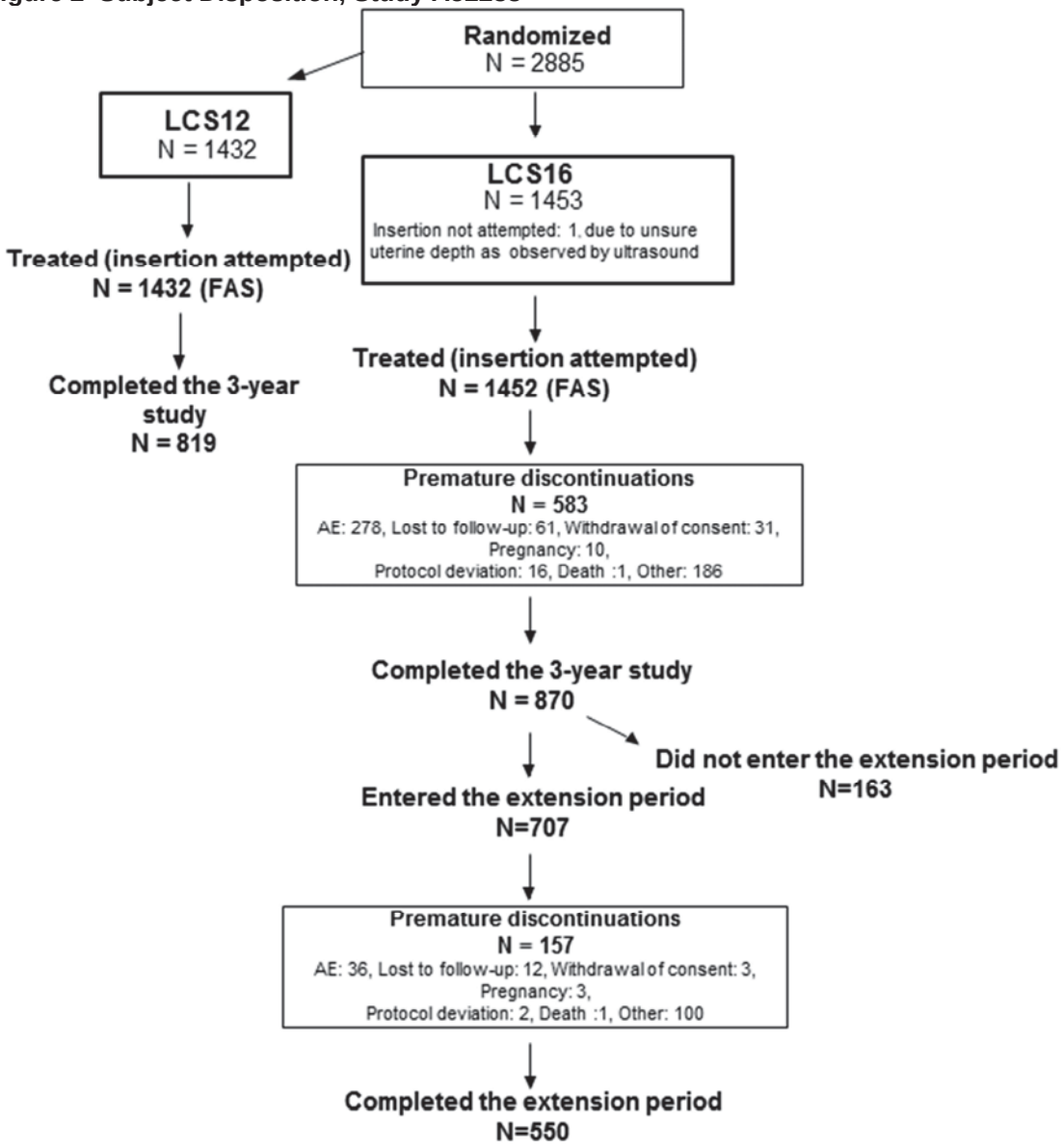
7.3 DISPOSITION OF SUBJECTS

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 1,452 receiving the LCS16. This constituted the FAS population. Of these, 563 (39%) were enrolled in the US and 92 (6%) in Canada.

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

Team Leader Comments

Figure 2 Subject Disposition, Study A52238



Source: CSR PH-37274, Figure 8-1, page 66

Table 3 Number and Reasons for Premature Discontinuation, Study A52238

Disposition	LCS 16 first 3 years N=1,453 n (%)	LCS16 extension (after 3 years) N=707 n (%)	LCS16 Overall N=1,453 n (%)
Screened	3,661		3,661
Study medication administered	1,452 (>99.9%)	707 (100%)	1,452 (>99.9%)
Randomized in US site	563 (38.8%)	198 (28.0%)	563 (38.8%)
Completed study phase (3 years or extension)	163 (11.2%)	550 (77.8%)	713 (49.1%)
Prematurely discontinued	583 (40.1%)	157 (22.2%)	738 (50.8%)
Reason for discontinuation			
Withdraw of consent	31 (2.1%)	3 (0.4%)	34 (2.3%)
Protocol deviation	16 (1.1%)	2 (0.3%)	18 (1.2%)
Adverse event	278 (19.1%)	36 (5.1%)	314 (21.6%)
Death	1 (<0.1%)	1 (0.1%)	2 (0.1%)
Lost to Follow-up	61 (4.2%)	12 (1.7%)	73 (5.0%)
Pregnancy	10 (0.7%)	3 (0.4%)	13 (0.9%)
Other	186 (12.8%)	100 (14.1%)	284 (19.6%)

Source: Table 3, Statistical review by Weiya Zhang, Ph.D., dated August 19, 2016

Team Leader Comments

- **Note that "Completed Study Phase" and "Prematurely Discontinued" for first 3 years are underestimates and overestimates, respectively, because they exclude the women who continued into the extension phase.**
- **Reasons included in the "other" category for women with the LCS16 were predominantly desire for pregnancy. Additional reasons in this category included moving, no further need for contraception, partner felt strings, accidental removal and failed insertion.**

The Applicant explored study discontinuations by parity. For the LCS16 arm, 26% of nulliparous women discontinued prematurely due to withdrawal of consent or an adverse event (AE), while 23% of parous women discontinued for one of these reasons. Withdrawals due to progestin-related effects, and "other" reasons were slightly higher among nulliparae, while withdrawals related to the bleeding profile did not vary by parity.

Team Leader Comment

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

7.4 EFFICACY FINDINGS

7.4.1 Assessment of Efficacy in Study A52238

Routine pregnancy testing was not done in the initial three-year phase of the study except during the end of treatment visit, at which time a urine test was performed before IUS removal. Routine pregnancy testing was added in the extension phase, at the end of Year 4 and Year 5. 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. Reported pregnancies were to be confirmed by ultrasound or serum pregnancy testing, with IUS removal recommended in the cases of confirmed pregnancies.

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's typical practice is that exposure time be expressed as 28-day cycles beginning from insertion and that cycles in which back-up contraception was used be considered non-evaluable. Based on the Division's request, Pearl Index calculations were provided based on both women-years (WY) and 28-day cycles, 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.

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, regardless of whether or not it was successful. Subjects were analyzed according to the actual IUS inserted (i.e., not as intent-to-treat for the six subjects [four randomized to LCS16 and two to LCS12] 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.

Team Leader Comment

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.

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 1-5 individually, and cumulative rates for each successive year. The unadjusted Pearl Index presented here was the primary outcome measure, and includes all exposure through removal or total expulsion of the LCS. The Applicant also calculated an adjusted Pearl Index, which considered the exposure time until the IUS was last known to be in situ (or displaced but still intrauterine).

The Applicant also conducted a secondary efficacy analysis using the Kaplan-Meier method. 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. These methods calculate pregnancy rates based on the number of women at risk in each point in time within a given time interval, rather than on the total number of cycles for a given year. For this reason, these analyses are often not directly comparable to the Pearl Index.

7.4.3 Primary Efficacy Results

A total of 13 on-treatment pregnancies occurred in subjects in Study A52238, with nine occurring on-treatment in parous women and four in nulliparae; details are shown in Table 4. Eight of the pregnancies were ectopic (including all four in the nulliparous women), two were spontaneously aborted (per the Applicant), one ended in a missed abortion and two resulted in healthy term infants. Timing from insertion to conception ranged from nine months to four years, three months. Two of the pregnancies occurred in the first year, four each in Year 2 and Year 3, one in Year 4 and two in Year 5.

There were no pre-treatment pregnancies. One additional pregnancy (Subject # 245406) occurred soon after treatment, 20 days after IUS expulsion; this was not included in the pregnancy rate calculations. In addition, there were four "post-study" pregnancies of which the site became aware, in women who had had negative pregnancy tests at the time of LCS removal and were subsequently lost to follow-up. In the absence of medical confirmation and dating information on these pregnancies, the Applicant did not include them as on-treatment pregnancies.

Table 4 Details of Pregnancies, LCS16 Arm

Study A52238			
Subject ID	**Exposure year**	**Parity**	**Outcome**
On-treatment pregnancies			
160423	Year 1 (9 months post-insertion)	Parous	**Ectopic pregnancy**; LCS noted by ultrasound to be **properly placed** at time of diagnosis, and was removed. Ectopic visualized in left fallopian tube and "resolved spontaneously."
243228	Year 1 (10 months post-insertion)	Parous	Subject discontinued from study due to right **ectopic pregnancy**, LCS noted by ultrasound to be **properly placed** at time of diagnosis, and was removed; urine pregnancy test was positive. She underwent laparoscopic right salpingostomy and recovered.
180112	Year 2	Parous	Subject had an incomplete **spontaneous abortion** and underwent uterine curettage and LCS removal; LCS noted to be **properly placed** by ultrasound prior to removal
180317	Year 2	Parous	Ultrasound showed LCS with **displaced intrauterine location**, left tubal **ectopic pregnancy** diagnosed. Subject underwent laparoscopic evacuation of pregnancy and IUS removal.
200609	Year 2	Parous	Subject discontinued from study due to "**ectopic mass**;" LCS noted by ultrasound to be **properly placed** at time of removal on 12/21/09. "Ectopic mass" first noted on 12/1/09; urine and serum pregnancy tests on 12/21/09 were both negative, but "pregnancy conception date was estimated for an unknown date in OCT 2009." Subject had previously reported severe abdominal pain and vaginal bleeding in early November 2009. "Early spontaneous termination happened on 21 DEC 2009."

Study A52238			
Subject ID	**Exposure year**	**Parity**	**Outcome**
242321	Year 2	Nulliparous	Subject discontinued due to SAEs of ruptured **ectopic pregnancy** and decreased hemoglobin; LCS noted by ultrasound to be **properly placed** at time of removal that same day. She underwent right laparoscopic salpingectomy and required blood transfusion.
160927	Year 3	Parous	Pregnancy diagnosed by hCG, with two empty amnion sacs visualized by ultrasound, diagnosed as **blighted ovum, with missed abortion.** Uterus evacuated the following day. LCS noted to be **properly placed** by ultrasound, and was removed.
243703	Year 3	Parous	Subject discontinued due to **total expulsion** on unknown date, followed by positive urine pregnancy test and ultrasound confirming pregnancy on 4/6/10. She delivered a **healthy term infant.**
243932	Year 3	Nulliparous	Subject discontinued due to **ectopic pregnancy**; LCS noted by ultrasound to be **properly placed** at time of removal that same day. Ectopic was treated with methotrexate and resolved.
244519	Year 3	Nulliparous	Subject discontinued due to **ectopic pregnancy;** LCS noted by ultrasound to be **properly placed** at time of removal that day. Subject was treated with Methotrexate and D&C. Note: unclear why subject received a D&C given a confirmed ectopic pregnancy; no details are provided about her course or resolution of the ectopic on Methotrexate.
170411	Year 4	Nulliparous	Subject entered extension phase and right **ectopic pregnancy** was diagnosed five months later. LCS noted by ultrasound to be **properly placed** at time of removal the day of diagnosis. Subject was treated with Methotrexate, with appropriate resolution of the ectopic over several months.
120324	Year 5	Parous	The subject entered the extension phase and had LCS location confirmed as intrauterine at that time. 17 months later, she had a positive urine pregnancy test confirmed by ultrasound, which also found the LCS to be **partially expelled**, into the cervical canal. The investigator could not determine whether the expulsion had preceded the pregnancy. The LCS was removed that day and she delivered a **healthy term infant.**
180616	Year 5	Parous	The subject was diagnosed with a **missed abortion**, of a 5-week gestation, when ultrasound found a gestational sac with amorphous material. LCS noted by ultrasound to be **properly placed** at time of removal the day of diagnosis. The subject underwent vacuum aspiration.
Subjects not considered by Applicant to have on-treatment pregnancies			
245406	Year 1 (7 months post-insertion)	Parous	The subject experienced LCS complete expulsion on 9/18/08, which was confirmed by ultrasound on 10/24/08. She had a positive urinary pregnancy test on 10/24/18; ultrasound on that day showed a thickened endometrium but no gestational sac. Subsequent ultrasound on 2/5/09 showed an estimated gestational age of 19 weeks, indicating an estimated date of conception of 10/8/18 (20 days post-expulsion).
241157*	Year 1	Parous	Subject discontinued the study due to desire for pregnancy. LCS removed and end-of-study pregnancy test was negative. No pregnancy was reported at 3-month follow-up call, but at 12-month follow-up call, subject reported a pregnancy with normal outcome, but did not provide dates. Attempts to reach the subject again were unsuccessful.
241189*	Year 1	Parous	Subject had negative pregnancy tests “during treatment” and

Study A52238			
Subject ID	**Exposure year**	**Parity**	**Outcome**
			discontinued the study due to desire for pregnancy. LCS removed following identification of correct localization, and end-of-study pregnancy test was negative. Subject was not reachable at 3-month follow-up call, but at 12-month follow-up call, she reported a pregnancy with normal outcome, but did not provide dates. Attempts to reach the subject again were unsuccessful.
244437	Year 5	Nulliparous	Subject entered extension phase and sixteen months later, she requested LCS removal for unspecified reasons. Ultrasound showed correct location of LCS and pregnancy test was negative at the time of removal. Subject reported a pregnancy at the 3-month follow-up call, but did not provide dates. Attempts to reach the subject again were unsuccessful.
246207	Year 2	Parous	Subject was discontinued due to an AE of pelvic pain; LCS found to be correctly situated on the day of removal (10/12/09) and pregnancy test was negative. Subject reported a pregnancy at the 3-month follow-up call, but did not provide dates. Approximately 5 months after that (on 6/2/10), the subject reported a normal pregnancy outcome, but did not provide date of delivery. Information reported later in response to an Information Request indicated that the subject had an ultrasound on 4/14/10, indicated a 20 week gestation, corresponding to an estimated date of conception of 12/9/09, well after removal.

Source: Narratives appended to Module 5.3.5.2 and Module 2.7.3

Team Leader Comments

- **Of the 13 pregnancies, 10 were associated with correct LCS placement, including seven of the eight of the ectopics and the missed/spontaneous abortions. Two of the remaining three cases, both of which resulted in a healthy term birth, were associated with total or partial expulsions. The remaining case, an ectopic pregnancy was noted to be in a "displaced intrauterine location," likely not at the fundus.**
- **Although Subject 160927 is characterized by the Applicant as having a spontaneous abortion, she actually had a missed abortion and underwent uterine evacuation per the narrative. Similarly, Subject 180112 was noted to have an incomplete spontaneous abortion and underwent uterine curettage. Therefore, aside from the two term deliveries, most of the women who became pregnant on the LCS16 required a surgical intervention, aside from two women with ectopics that reported resolved spontaneously, and two who were managed medically with Methotrexate. One nulliparous woman required a salpingectomy; it appears that the other women with ectopic pregnancies were able to preserve their fallopian tubes.**
- **I agree that Subject 245406 conceived post-treatment.**
- **Although follow-up information on Subject 240115 was insufficient, I do not believe she is likely to represent an on-treatment pregnancy. In the case of Subjects 241189 and 244437, the absence of, or limited information at, the 3-month follow-up, respectively, makes determination of the likely date of conception more problematic; however, I concur that they should not be considered an on-treatment pregnancy due to the findings at their end-of-study visits.**
- **In the case of Subject 246207, however, if she had a term pregnancy, it appears that she may have conceived on-treatment. Delivery of a 37-week gestation on or before June 2, 2010 would give an estimated date of conception on or before**

September 30, 2009. It is possible that the pregnancy test on October 12, 2009 could have been negative with such a date of conception.

An information request was sent to the Applicant, who indicated it had become aware of an April 14, 2010 ultrasound report that gave a gestational age corresponding to a post-treatment conception. The Pregnancy Report and Pregnancy Outcome Forms were reportedly completed more than a year after the follow-up call, and the indication that delivery had occurred reflected the form completer's assumption regarding the pregnancy status at the time the forms were completed. While this scenario reflects poor record keeping, I concur that this was not an on-treatment pregnancy.

Pearl Index

The statistical reviewer, Weiya Zhang, Ph.D., reviewed the Applicant's data and confirmed the reported Pearl Index (see Table 5), using exposure based on 28-day cycles. These calculations are virtually identical to the Applicant's primary analysis based on women-years. Her calculations give a Pearl Index of 0.16 (upper bound of the 95% confidence interval [CI] is 0.58) in the first year of use, with relatively similar values each successive year. The cumulative 5-year Pearl Index (95% CI upper bound) based on 28-day cycles was 0.29 (0.50).

Table 5 Pearl Index Calculation, Pregnancies in Woman aged 18-35 Years, 28-day Cycles

Time	Subjects N	Pregnancies n	Relevant exposure cycles	Pearl Index	95% CI
Overall	1414	13	57335	0.29	0.16, 0.50
Year 1	1414	2	16207	0.16	0.02, 0.58
Year 2	1182	4	13853	0.38	0.10, 0.96
Year 3	990	4	11610	0.45	0.12, 1.15
Year 4	717	1	8556	0.15	0.00, 0.85
Year 5	623	2	7087	0.37	0.04, 1.33
2 years	1414	6	30060	0.26	0.10, 0.56
3 years	1414	10	41670	0.31	0.15, 0.57
4 years	1414	11	50226	0.28	0.14, 0.51
5 years	1414	13	57313	0.29	0.16, 0.50

Source: Table 6, Statistical review by Weiya Zhang, Ph.D., dated August 19, 2016, confirming data in Table 1.2/27 in the Integrated Summary of Efficacy

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. Pearl Index calculations were also made (see Table 5), but Dr. Zhang 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.

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

Time	Subjects N	Pregnancies n	Relevant exposure WY	Kaplan-Meier Rate	95% CI
Year 1	1452	2	1252.43	0.178	0.044, 0.709
Year 2	1206	4	1066.87	0.371	0.139, 0.988
Year 3	1010	4	897.75	0.423	0.159, 1.123
Year 4	773	1	659.17	0.147	0.021, 1.038
Year 5	636	2	558.30	0.333	0.083, 1.324
2 years	1452	6	2319.30	0.540	0.242, 1.202
3 years	1452	10	3217.05	0.957	0.514, 1.779
4 years	1452	11	3876.22	1.102	0.605, 2.004
5 years	1452	13	4434.53	1.445	0.823, 2.531

Source: Table 7, Statistical review by Weiya Zhang, Ph.D., dated August 19, 2016, confirming data in Table 9-3 in the clinical study report

Team Leader Comment

While the per-year pregnancy rates are similar for the Pearl Index and Kaplan-Meier calculations, after Year 1, the cumulative estimates begin to diverge due to differences in calculating the exposure cohort. Based on Dr. Zhang's recommendation, the labeled cumulative five-year pregnancy rate should reflect the Kaplan-Meier estimate.

Dr. Zhang also calculated pregnancy rates with the exclusion of the two terminated sites (2415 and 2434; see Section 11) as a sensitivity analysis. The Year 1 Pearl Index was 0.16 with an upper bound of 0.59, compared to 0.16 with an upper bound of 0.58 when these sites are included. The five-year cumulative Kaplan-Meier rate was 1.46 with an upper bound of 2.55 when these sites were excluded, compared to 1.45 (2.53) when they are included.

Team Leader Comment

The pregnancy rate either in Year 1 or overall is not significantly impacted by the exclusion of the two sites that were terminated. As was done for Skyla labeling, the pregnancy rates reported in labeling will reflect all study sites.

Dr. Zhang 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 Cumulative 5-Year Pearl Index by Age, Parity, BMI and US/Non-US Subgroups, 28-day Cycle Analysis

Category	Subjects N	Pregnancies n	Relevant exposure WY	Pearl Index	95% CI
Age					
18-25 years	564	3	1628.76	0.18	0.04, 0.54
>25-35 years	888	10	2808.55	0.36	0.17, 0.66
Parity					
Nulliparous	574	4	1636.80	0.24	0.07, 0.63
Parous	878	9	2800.51	0.32	0.15, 0.61
BMI					
<30 kg/m^2	1198	9	3703.97	0.24	0.11, 0.46
≥30 kg/m^2	250	4	721.27	0.55	0.15, 1.42
Region					
US	563	5	1446.95	0.35	0.11, 0.81
Non-US	889	8	2990.36	0.27	0.12, 0.53

Source: Table 9-2 in the clinical study report and reviewer's analysis.

Source: Table 8, Statistical review by Weiya Zhang, Ph.D., dated August 19, 2016

Team Leader Comments

- **Overall, there were over 16,000 cycles of exposure to LCS16 in Year 1 that were evaluable for efficacy (see Table 5).**
- **Although the Pearl Index is numerically higher for older users, parous women, higher BMI users and US women, confidence intervals overlapped across strata in each subgroup analysis.**
- **The overall Pearl Index, as well as that for the subgroup of US subjects, provides evidence of acceptable contraceptive efficacy for a five-year duration of treatment.**

Statistician's Conclusion

Dr. Zhang confirmed the Applicant's overall primary efficacy findings, using both a woman-year and a 28-day cycle-based calculation. Results were almost identical using either timeframe.

Dr. Zhang made the following conclusions and recommendations regarding contraceptive efficacy in her review dated August 19, 2016:

> *There were no statistical issues identified in this submission. The pregnancy rates were estimated by the Pearl Index (PI) with its 95% confidence interval (CI) and Kaplan-Meier method. The 5 year PI was 0.29 (95% CI: 0.16, 0.50) and yearly rates were 0.16 (95% CI: 0.02, 0.58), 0.37(95% CI: 0.10, 0.96), 0.45 (95% CI: 0.12, 1.14), and 0.15 (95% CI: 0.00, 0.85) for Year 1, 2, 3, 4, and 5, respectively. The cumulative 5-year pregnancy rate using Kaplan-Meier method was 1.4 (95% CI: 0.82 to 2.53) per 100 women.*
>
> *From a statistical perspective, this study provided evidence supporting the efficacy of LCS16 for the prevention of pregnancy for up to 5 years in women 18 to 35 years of age.*

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. Diaries that ended before completion of a 90-day reference period were evaluated, using a proportional correction factor, if they included at least 60 days of data.

The Applicant reported bleeding data using the 90-day reference period recommended by the WHO, starting with the day of insertion as well as by 28-day reference periods, as the Division requested. 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.

Based on 90-day reference periods, women who received LCS16 had a 5.3% rate of amenorrhea in the second period, 12% by the fourth (end of Year 1), 17.5% by end of Year 2, 19.9% by end of Year 3, and 22.6% at the end of Years 4 and 5. After the first 90-day period, rates of "infrequent bleeding" (1-2 bleeding/spotting episodes per 90-day period) remained fairly constant at about 20-30% throughout the five years of treatment, "frequent bleeding" (> 5 bleeding/spotting episodes per 90-day period) decreased from about 10% in the second 90-day period to 2% by the end of Year 5, "irregular bleeding" (3-5 bleeding episodes and < 3 bleeding/spotting-free intervals of ≥ 14 days) decreased from 25% in the second period to 9.4% at the end of Year 5, and "prolonged bleeding" (bleeding/spotting episodes lasting > 14 days) decreased from 13.7% to 1.1% over the same interval.

Table 8 Bleeding/spotting Days per 28-Day Cycle

Cycle	N	Mean (SD)	Min	Median	Max
1	1,619	15.9 (7.6)	0	16.0	28
2	1,619	12.4 (7.5)	0	11.0	28
3	1,600	9.3 (6.7)	0	8.0	28
4	1,575	7.8 (6.0)	0	7.0	28
7	1,518	5.7 (4.9)	0	5.0	28
13	1,394	4.4 (4.2)	0	4.0	28
20	1,262	3.8 (3.8)	0	3.0	23
26	1,167	3.5 (3.7)	0	3.0	27
33	1,053	3.5 (3.6)	0	3.0	28
39	913	3.3 (3.5)	0	3.0	24
46	659	3.0 (3.1)	0	3.0	18
52	623	3.1 (3.2)	0	3.0	19
59	570	2.9 (3.2)	0	2.0	20
65	322	3.0 (3.1)	0	3.0	15

Source: Summary of Clinical Efficacy:2, Table 3-46, page 100 and [iss.ise-iss.pdf:3], Table 1.2/39, pp 1207-8

Table 9 Spotting Days per 28-Day Cycle

Cycle	N	Mean (SD)	Min	Median	Max
1	1,619	8.6 (6.0)	0	8.0	28
2	1,619	7.1 (5.9)	0	6.0	28
3	1,600	5.3 (5.0)	0	4.0	28
4	1,575	4.6 (4.4)	0	4.0	28
7	1,518	3.5 (3.4)	0	3.0	24
13	1,394	2.9 (3.0)	0	2.0	28
20	1,262	2.6 (2.8)	0	2.0	18
26	1,167	2.3 (2.7)	0	2.0	19
33	1,053	2.4 (2.6)	0	2.0	15
39	913	2.2 (2.6)	0	2.0	16
46	659	2.0 (2.3)	0	1.0	18
52	623	2.1 (2.3)	0	2.0	15
59	570	2.0 (2.3)	0	1.0	14
65	322	2.1 (2.4)	0	2.0	15

Source: Summary of Clinical Efficacy:2, Table 3-46, page 100 and [iss.ise-iss.pdf:3], Table 1.2/45, pp 1227-8

Team Leader Comments:

- **As was done in Skyla labeling, the bleeding profile described in the labeling will reflect the pooled data from both trials.**
- **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.**

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 LCS16 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. Based on pooled data for the LCS16 arm, ovulation was identified in 23 of 26 women in Year 1, in 19 of 20 in Year 2, and in all 16 women in Year 3. The single woman still in the subset at Year 4 ovulated; no subjects remained under study at Year 5. These results did not vary according to the progesterone cut-off used.

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

Team Leader Comment:

LCS16 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. For all three IUSs combined (LCS12, LCS16, and Mirena), 96.4% of subjects had successful insertion; for the LCS16 the overall insertion success rate was 96.1%. The first insertion was successful in 96.1% of women; of the 66 in whom it failed, 61 had a second attempt, which was successful in 96.7%. Of the 68 total insertions that failed on the first or second attempt, 63% were attributable to inserter problems (IUS or inserter became unsterile - 4, IUS came out immediately after insertion - 25, malfunction -14), 16% to patient problems (tight cervix - 8, small uterus - 1, vasovagal attack - 1, uterine position - 1), and the remaining 21% to unspecified other (14) reasons. Of failed first insertions, 44% occurred in nulliparae; overall rates of success by parity were 95.4% (619/649) for nulliparous women and 96.6% (1,071/1,109) for parous women.

Local anesthesia was used in 8.7% of LCS16 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 LCS12 and LCS16 insertions rated "easy" compared to 75% of Mirena insertions, and approximately 2% of all IUS insertions rated as "very difficult." In comparison, for parous women, insertion was rated as "easy" for 94% of LCS 12 and LCS16 insertions, and as "very difficult" for only 0.6 and 0.7%, respectively. Comparable ratings for Mirena indicated slightly more difficult insertions even in parous women.

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 88% (LCS16) to 91% (LCS12) rated as "easy." For the LCS arms, 2% were assessed as "very difficult" compared to none in the Mirena arm. Parity did not affect the investigators' assessments of removal ease. Subjects' evaluations of pain during removal varied by parity: for the LCS16, 70% of nulliparous women rated pain as none to mild, compared to 87% of parous women, with 4% and 2%, respectively, rating pain as "severe."

Information about insertion of the Skyla IUS using the to-be-marketed (b) (4) inserter is discussed in Section 8.8.2.

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 LCS16 in the prevention of pregnancy. The annual PI showed no consistent trend toward increasing with successive years of treatment (0.16, 0.38, 0.45, 0. 15 and 0.37 in Years 1 through 5, respectively), and the cumulative pregnancy rate over the five-year course of treatment by Kaplan-Meier analysis was 1.45. The cumulative rate at three years is 0.96, very similar to that of Skyla (0.89) in the same trial. 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 AEs) and ratings of pain, particularly with insertion, are slightly 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 over 5,225 women-years (about 68,000 28-day treatment cycles) for LCS16, over 24,000 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. Based on the pooled database, which primarily reflects the phase 3 study, the Applicant met these requests, with 19,895 cycles in the first year, and 550 women who completed five years. Almost 7,500 of the cycles in the first year and almost 24,000 overall were from North American subjects.

Table 10 Exposure by Study, Treatment Arm and Parity

Study	Study A52238		Study A46796			Pooled		
Arm	LCS12	LCS16	LCS12	LCS16	Mirena	LCS12	LCS16	Mirena
28-day cycles*								
Total	41,961	**60,142**	7,844	**7,977**	8,186	49,805	**68,118**	8,186
Nulliparous	15,800	**22,587**	1,430	**1,510**	1,625	17,230	**24,096**	1,625
Parous	26,161	**37,555**	6,414	**6,467**	6,561	32,575	**44,022**	6,561
Women-Years								
Total	3,219	**4,614**	602	**612**	628	3,821	**5,225**	628
Nulliparous	1,212	**1,733**	110	**116**	125	1,322	**1,848**	125
Parous	2,007	**2,881**	492	**496**	503	2,499	**3,377**	503

Source: Based on Response to Information Request, submitted on September 15, 2016

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 LCS16 subjects. In addition, it should be noted that data for LCS12 and Mirena are based on three years of exposure, while LCS16 data are reported over the full five years of exposure, including the extension phase of Study A52238.

8.1 DEATHS AND SERIOUS ADVERSE EVENTS

Deaths

Two deaths occurred in Study A52238, a suicide in a 20 year old woman who received LCS16 in January 2008, and another subject who received LCS 16 and was killed in a bicycle/motorcycle collision. Subject 210112, the suicide, 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. Neither death was considered by the investigators 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.

There were no deaths in the phase 2 study.

Serious Adverse Events

There were a total of 98 women who received LCS16 (5.8%) with SAEs in the pooled database; 86 women (5.9%) in Study A52238 and 12 (4.9%) in Study A46796. Comparable rates were 4.7% for LCS12 pooled population, and 6.3% for Mirena (phase 2 study only). The Applicant reported that 1.3% of women had drug-related SAEs (ectopic pregnancy, PID, pregnancy loss, uterine perforation, ovarian cyst and abdominal pain). Selected potential serious adverse reactions (SARs; i.e., SAEs that might possibly be related to study drug in my opinion) are shown in Table 11 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	LCS16 5-year N = 1,697		LCS12 3-year N = 1,672		Mirena 3-year N = 256	
	n	%	n	%	n	%
Total likely SARs	37	2.2	N/A			
Ectopic pregnancy/ruptured ectopic pregnancy	10	0.6	4	0.2	0	
PID or tubo-ovarian abscess	6	0.4	3	0.2	1	0.4
Abdominal pain	4	0.2	4	0.2	1	0.4
Depression or affective disorder	4	0.2	1	< 0.1	0	
Ovarian cyst, ovarian cyst ruptured, ovarian cyst torsion or hemorrhagic ovarian cyst	4	0.2	4	0.2	5	2.0
Spontaneous abortion or incomplete spontaneous abortion or missed abortion or blighted ovum	4	0.2	3	0.2	0	
Uterine perforation (includes one coded as "device dislocation"	3	0.2	0		0	
Completed suicide, suicide attempt or depression, suicidal	1	< 0.1	2	0.1	0	
Hypertension	1	< 0.1	1	< 0.1	0	
Deep vein thrombosis	0		1	< 0.1	0	
Vaginal hemorrhage	0		0		1	0.4
Weight increased	0		1	< 0.1	0	

Source: Based on Integrated Summaries of Efficacy and Safety: 2, Table 1.3/19, pp 1652-8

There were several SAEs related to suicidality or depression in the LCS16 arm:

- Subject 160972 had an SAE of depression in the fourth year of study participation. She had a history of mild depression upon entry and experienced worsening depression about three years post-insertion, which was treated with medication. Five months later, she was hospitalized for about two weeks with worsened depression, and released with new medication and psychotherapy. She remained in the study and completed the extension phase.
- 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 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.
- Subject 244437 had an SAE of severe depression about 3.5 years after insertion. She had reported a history of mild depression, anxiety and bipolar disorder since 1995. She entered the extension phase, but was hospitalized for four days for severe premenstrual depression and began having suicidal ideation while hospitalized. Her

medications were changed and the suicidal ideation resolved; however, she continued having premenstrual depression.

- Subject 210112 is described above under Deaths.

Subject 242813 completed the extension phase and was then admitted to the hospital one week after LCS removal with severe uncontrolled hypertension (198/102). She had not reported a history of hypertension, but had a blood pressure of 128/88 at screening. It is not reported whether she had elevated pressures during periodic monitoring during the trial.

Subject 160978 (coded as "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. There were two other reported uterine perforations noted at the End of Extension visit.

In addition to the possibly drug-related SAEs, cases of hypersensitivity and anaphylaxis were to amoxicillin and shellfish, respectively, and therefore, are unrelated to the LCS products. Adhesions were reported in Subject 180117. She 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 180521 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.

The rate of SAEs remained steady for the first three years of exposure, and decreased slightly in the final two years of the phase 3 study.

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.**
- **Including the suicide, there are five cases of worsened depression while using LCS16; while clear histories of depression were not noted for all subjects prior to study entry, it appears that almost all had some mental health issues prior to LCS insertion.**
- **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, 375 LCS16 subjects (22.1%) discontinued prematurely due to an AE. The listing by study of AEs that caused discontinuation in ≥ 0.5% of subjects in either LCS treatment arm is presented in Table 12. The rate of AE discontinuations decreased over years of exposure. Discontinuations by parity are discussed in Section 0.

Table 12 AEs leading to Premature Withdrawal (≥ 0.5%), Pooled Dataset

AE leading to withdrawal	LCS16 5 years N=1,697		LCS12 3 years N=1,672	
	N	%	N	%
Any Event	375	22.1	361	21.6
Vaginal, genital, uterine hemorrhage, dysfunctional uterine bleeding, menstrual disorder, menstruation irregular, menometrorrhagia, menorrhagia, metrorrhagia or polymenorrhea	76	4.5	78	4.7
Device expulsion or dislocation*	51	3.0	48	2.9
Pelvic pain or pelvic discomfort	46	2.7	30	1.8
Acne or acne cystic or seborrhea	39	2.3	49	2.9
Abdominal or lower abdominal pain	29	1.7	42	2.5
Dysmenorrhea or uterine spasm	22	1.3	32	1.9
Weight increased	21	1.2	11	0.7
Mood altered or mood swings	15	0.9	14	0.8
Ovarian cyst or hemorrhagic ovarian cyst	11	0.6	6	0.4
PID or endometritis or salpingo-oophoritis or tubo-ovarian abscess	11	0.6	9	0.5
Libido decreased or loss of libido	10	0.6	9	0.5
Dyspareunia	10	0.6	9	0.5
Ectopic pregnancy or ruptured ectopic pregnancy	9	0.5	4	0.2
Headache or migraine or tension headache	9	0.5	9	0.5
Breast discomfort, breast pain or breast tenderness	5	0.3	8	0.5
Depression or depressed mood	5	0.3	10	0.6
Abdominal distension	4	0.2	8	0.5

*** excludes one AE reported as "device dislocation" in the LCS16 arm that actually represented a myometrial perforation**
Source: Based on Integrated Summaries of Efficacy and Safety, Table 1.3/22, pp 1737-42

Team Leader Comments:

- **Rates for specific events are slightly different than those reported by the Applicant because related terms that did not reach the 0.5% threshold have been included here.**
- **In general, despite the longer duration of exposure to LCS16, rates of discontinuations due to AEs were quite similar for LCS16 and LCS12.**

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. In addition, in the phase 2 study, a normal pregnancy was still considered an AE. AEs that are clearly unrelated to Kyleena (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

	LCS16 N=1,697 n (%)	LCS12 N=1,672 n (%)	Mirena N=256 n (%)
Vulvovaginitis	412 (24.3)	337 (20.2)	NA
Hemorrhagic cyst or hemorrhagic ovarian cyst or ovarian cyst/ovarian cyst ruptured or ovarian cyst torsion	395 (23.3)	225 (13.5)	65 (25.4)
Cluster headache or headache/migraine or migraine with aura or migraine without aura or tension headache	276 (16.3)	252 (15.1)	89 (34.8)
Acne or acne cystic or seborrhea	271 (16.0)	253 (15.1)	94 (36.7)
Abdominal pain or abdominal pain lower or abdominal pain upper or abdominal tenderness	232 (13.7)	212 (12.7)	47 (18.4)
Breast discomfort or breast pain or breast tenderness	184 (10.8)	145 (8.7)	92 (35.9)
Dysmenorrhea or uterine spasm	176 (10.4)	177 (10.6)	19 (7.4)
Pelvic discomfort/pelvic pain	140 (8.2)	106 (6.3)	1 (0.4)
Cervix hemorrhage uterine or dysfunctional uterine bleeding or genital hemorrhage or menometrorrhagia or menorrhagia or menstruation irregular metrorrhagia or polymenorrhea or uterine hemorrhage or vaginal hemorrhage	135 (8.0)	141 (8.4)	8 (3.1)
Nausea	79 (4.7)	92 (5.5)	22 (8.6)
Affective disorder or depressed mood or depression or depression suicidal or depressive symptom	78 (4.6)	74 (4.4)	10 (3.9)
Genital discharge or vaginal discharge	77 (4.5)	69 (4.1)	4 (1.6)
Device expulsion or dislocation*	53 (3.1)	49 (2.9)	4 (1.6)

*** excludes one AE reported as "device dislocation" in the LCS16 arm that actually represented a myometrial perforation**
Source: Based on Integrated Summaries of Efficacy and Safety: 2, Table 1.3/7, pp 69-101

The proportion of women who reported an AE generally decreased over time; for the LCS16 arm, 75% of subjects had an AE in Year 1, 55% in Year 2, 52% in Year 3, 39% in Year 4 and 45% in Year 5.

Overall, AEs occurred somewhat more frequently in nulliparous women. AEs likely to have been drug-related in the pooled database for LCS16 that were more common in nulliparae were acne (17% vs. 12%), dysmenorrhea (12% vs. 6%), and pelvic pain (11% vs. 6%). Ovarian cysts were slightly less common (20 vs. 22%).

Team Leader Comments:

- **The markedly higher rates of breast complaints and acne/seborrhea in the Mirena arm reflect the directed questioning about such symptoms in the phase 2 trial (the only trial with a Mirena arm).**
- **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

Ten subjects (0.6%) had ectopic pregnancies in the LCS16 arm and four (0.2%) in the LCS12 arm; no ectopics occurred in the Mirena arm of the pooled dataset. In the LCS16 group, two occurred in Year 1, four in Year 2, three in Year 3, one in Year 4 and none in Year 5. In the LCS16 arm, five ectopic pregnancies occurred in nulliparous subjects and five in parous women; making the rate nominally higher in nulliparous women (0.8% vs. 0.5% in parous women).

Of total pregnancies, 50% (eight of 13 in phase 3 and two of seven in phase 2) in the LCS16 arm were ectopic. The Applicant calculated Pearl Indices for ectopic pregnancy (Table 14). Dr. Zhou also calculated the Pearl Index for ectopic pregnancy in the phase 3 study by subgroups of age, parity, BMI and US vs. non-US region. There was no difference by age; rates were nominally higher for nulliparous women (0.24 vs. 0.14 for parous women), women with BMI $\geq$ 30 (0.28 vs. 0.16 for women with BMI < 30) and US women (0.28 vs. 0.13 for non-US women), but in all cases, the CIs overlapped.

Table 14 Ectopic Pregnancy Rates per Study and Pooled Data

	LCS16		LCS12	
	Number of Ectopic Pregnancies	Pearl Index*	Number of Ectopic Pregnancies	Pearl Index*
Study A52238	8	0.18	3	0.10
Study A46796	2	0.33	1	0.17
Pooled	10	0.20	4	0.11

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

Outcomes of the ectopic pregnancies in the LCS16 arm were three laparoscopic salpingectomies and two laparoscopic removals of the ectopic pregnancy. Two were managed expectantly and three were treated medically with methotrexate. The single ruptured ectopic pregnancy occurred in the LCS16 arm.

Team Leader Comments:

- **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.**

- **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, expressed as a Pearl Index, is low regardless of parity, not exceeding 0.3%.**

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.

A MedDRA Term Grouping search of related terms, including PID, endometritis, tubo-ovarian abscess, etc., was used to identify PID AEs. In the pooled dataset, nine women who received LCS16 (0.5%) had PID, as did six (0.4%) in the LCS12 arm and one (0.4%) in the Mirena arm. Of the nine LCS cases, eight were coded as PID and one as salpingo-oophoritis. Six were classified as SAEs.

Eight cases occurred in the phase 3 trials, and one in the phase 2 trial. Seven of the cases occurred in parous women. Six cases occurred in Year 1 (ranging from 1-2 days to 11 months post-insertion), one in Year 3 and two in Year 4.

Cases of endometritis that did not meet criteria for PID were also assessed. There were 13 cases in the LCS16 arm (0.8%), with 10 of these occurring in the first year post-insertion. Nine 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 Kyleena 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. Three partial uterine perforations (0.2%) were reported in women who received the LCS16 in the phase 3 study. One, coded as "device dislocation," (Subject 160978) was noted at the Year 2 visit, when the LCS was observed on ultrasound to be partially embedded within the myometrium; it was removed vaginally. The other two (Subjects 120629 and 245930) were incidentally identified during the End of Extension visit; both LCSs were removed successfully.

There were no perforations in the phase 2 study.

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 15 shows the frequency of expulsion by study and study arm; the Applicant noted that erroneously, not all expulsions were categorized as AEs; therefore, ultrasound examination data were used to

calculate the expulsion rates. Of the 59 cases, 54 were reported as AEs, with 48 classified as "device expulsion" and six as "device dislocation." Total expulsion occurred in 22 cases (37%) and partial in 37 cases (63%). More than half occurred in the first year post-insertion and the majority (85%) by Year 3.

Table 15 Percent of Women with Total or Partial Expulsions

	LCS16 n (%)	LCS12 n (%)	Mirena n (%)
Study A52238	54 (3.7)	53 (3.7)	NA
Study A46796	5 (2.0)	1 (0.4)	5 (2.0%)
Pooled	59 (3.5)	54 (3.2)	5 (2.0%)

Source: Based on Summary of Clinical Safety, Table 4-3, p 161

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; for LCS16 the cumulative probability of expulsion at Month 60 in parous women was 2.7%, compared to 0.4% for nulliparous women.

Team Leader Comment:
Given past 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 13-14% of women in the LCS16 arm of the phase 3 study had ovarian cysts at baseline that did not preclude enrollment. Because one site reported implausible values, or reported follicles as small cysts, the Applicant excluded women from this site from the counts. The proportion of abnormal ovarian cysts on ultrasound initially increased from baseline (18-19% at Month 6, and then decreased over time (6% at the End of Extension visit). Reported frequency of ultrasound-detected ovarian cysts was much lower for both LCS arms and over all time periods in the phase 2 study.

Ovarian cysts over 3 cm were to be reported as AEs. In the pooled dataset, 393 LCS16 women (23.2%) reported AEs of ovarian cyst, hemorrhagic ovarian cyst, ovarian cyst rupture or ovarian cyst torsion on treatment, compared to 225 (13.5%) in the LCS12 arm and 64 (25%) in the Mirena arm. Although most cysts were non-serious and resolved spontaneously, in four women in the LCS16 arm, cysts were reported as SAEs and seven women withdrew from the study due to ovarian cysts.

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. Abnormal epithelial cell findings were seen in 1.7% of women at Screening and 4.3% at End of Study. Because there were very few findings in Study A46796, results for the LCS16 arm of Study A52238 are presented in Table 16.

Table 16 Abnormal Pap Smear Results, Study A52238

	Screening N=1,443 n (%)	Month 12 N=1,169 n (%)	Month 24 N=978 n (%)	Month 36 N=1,312 n (%)	Month 48 N=615 n (%)	Month 60/ End of Study N=680 n (%)
# with abnormal Pap smear (% of N)	24 (1.7)	47 (4.0)	62 (6.3)	54 (4.1)	25 (4.1)	29 (4.3)
ASCUS	17 (65.4)	15 (31.3)	25 (40.3)	15 (27.8)	6 (24.0)	11 (37.9)
ASC-H	0	0	0	0	1 (4.0)	1 (3.4)
LSIL	8 (30.8)	26 (54.2)	25 (40.3)	31 (57.4)	14 (56.0)	15 (51.7)
HSIL	1 (3.8)	6 (12.5)	11 (17.7)	8 (14.8)	4 (16.0)	2 (6.9)
Squamous cell Ca	0	0	0	0	0	0

Percents represent proportion of total # with abnormal Paps; numbers may not equal total due to occasional missing results
Source: Based on Summary of Clinical Safety, Tables 4-18 & 4-20, pp 172 & 175

Team Leader Comment:
Although the proportion of abnormal Paps with high-grade lesions appears to increase over the duration of treatment, the absolute proportion of women with HSIL is low (0.3%) at the End of Study visit. This is consistent with the background rate of HSIL in the US population[3]

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 the phase 2 study, 8 of 11 LCS16 women (72.7%) who desired pregnancy had become pregnant by the 12-month follow-up.

The Applicant reported that in Study A52238, 179 women the LCS16 had discontinued because of a desire to become pregnant, and 163 (91%) of these had been contacted. Of these women 116 (71.2%) became pregnant within one year of discontinuing LCS.

For the pooled data, therefore, the pregnancy rate in the LCS16 arm was 124 of 174 women followed (71.3%).

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 rate of pregnancies among the total population suggests that there is no lasting impact on fertility.

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 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 women.

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

The highest number of abnormalities (6 women in the LCS16 arm) were reported at the End of Extension visit; these included fluid in the cavity, intrauterine pregnancies, myomas and polyps.

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

8.4.2 Bone Mineral Density

BMD (lumbar spine and total hip) was evaluated by dual x-ray absorptiometry (DXA) 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 17.

Table 17 Bone Mineral Density, Study A52238

	LCS16		LCS12	
	Lumbar Spine	Total Hip	Lumbar Spine	Total Hip
Baseline - N	103	102	102	102
Baseline mean	1.18	1.02	1.18	1.04
Month 36/End of study - N	71	71	80	80
Month 36/End of study mean	1.21	1.04	1.21	1.05
Month 36/End of study change from baseline	0.03	0.02	0.02	0.01
Month 60/End of study - N	37	37	NA	NA
Month 60/End of study mean	1.22	1.05	NA	NA
Month 60/End of study change from baseline	0.03	0.02	NA	NA

BMD- bone mineral density; EoS - End of Study; measurements are in g/cm2
Source: Based on Summary of Clinical Safety, Tables 4-23 and 4-24, pp 182-3

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 LCS16 has any significant impact on BMD.

8.5 LABORATORY TESTING & VITAL SIGNS

Safety laboratory evaluations were conducted at Screening, Month 36, and End of Study for serum chemistry, liver enzymes, hematology, urinalysis, lipid parameters and hemoglobin A1C. Most values were within normal limits at all assessments, and changes from baseline were small and generally similar across treatment groups (LCS16, Skyla and Mirena). The only parameter that showed an increase on treatment in the proportion of women with clinically significant laboratory findings was GGT (increases observed in 4% of LCS16 users at Year 5, compared to 3.1% of Skyla users and 4.9% of Mirena users at Year 3). There were adverse changes in lipids in a small proportion of subjects, as shown:

- Total cholesterol, changed from low/normal to high: 1.0% at Month 36, 1.3% at End of Extension
- HDL cholesterol, changed from normal/high to low: 5.3% at Month 36, 2.8% at End of Extension

- LDL cholesterol, changed from low/normal to high: 1.1% at Month 36, 1.5% at End of Extension
- Triglycerides, changed from low/normal to high: 2.7% at Month 36, 3.5% at End of Extension

Blood pressure, heart rate and weight were evaluated at Screening and at Month 12, 24 and 36, and at Month 48 and end of study for women in the extension phase. No relevant changes were noted. The mean change in weight at Year 3 was 1 kg for LCS16, compared to 0.6 kg for Skyla and 1.4 kg for Mirena.

Team Leader Comment:
The slight changes in certain laboratory values and weight are not of clinical concern.

8.6 POSTMARKETING SAFETY FINDINGS

No postmarketing safety data are available for LCS16 because it has not been approved anywhere at the time of this review (as discussed in Section 8.8.1, the LCS16 was submitted in parallel to the European Union (b) (4) Bayer updated the Company Core Data Sheet (CCDS) regarding risk factors for uterine perforation, based on the results of the EURAS IUD safety surveillance study (see additional discussion below). The company responded to a request from the Singapore regulatory body to issue a Dear Healthcare Professional Letter relating to this update.

In addition, a post-approval safety study (EURAS-LCS12) for Jaydess (as Skyla is known abroad) was approved by EU authorities in April 2014.

During the PSUR interval, the cumulative number of insertions of Mirena was estimated at almost (b) (4) million, with almost (b) (4) million WY of exposure. Mirena is marketed in 113 countries. For Skyla/Jaydess, over (b) (4) units have been sold since product launch, and the cumulative post-marketing exposure is over (b) (4) WY. Skyla/Jadesse is marketed in 33 countries. The only relevant ongoing studies are the three with LCS12 and the (b) (4) inserter discussed in Section 8.8.2.

Safety issues that remain closely monitored include uterine perforation, PID, risks associated with intrauterine pregnancy with LCS in situ, ectopic pregnancy, expulsion, ovarian cysts, and bleeding changes.

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

The Applicant concluded that no information available during the period of the PSUR impacted the benefit/risk profile of these LCSs.

Team Leader Comment:
The postmarketing information from Mirena and Skyla does not suggest any additional safety concerns relevant to Kyleena.

(b) (4) the risk of uterine perforation in postpartum women, based on the results of a European postmarketing study of Mirena (EURAS-IUD). The study's results suggested that that there

is an increased risk of uterine perforation in women who are breastfeeding and women who are up to 36 weeks postpartum at the time of levonorgestrel-releasing IUS insertion.

(b) (4)

The Applicant submitted another labeling supplement to both NDAs in June 2016, proposing the following revisions to labeling relating to perforation (deletions shown in strikethrough; new language underlined):

(b) (4)

The risk of perforation may be increased if Mirena is inserted when the uterus is fixed retroverted or not completely involuted (b) (4) Delay Mirena insertion a minimum of six weeks or until involution is complete following a delivery or a second trimester abortion.

(b) (4)

The current labeling supplements are under review, and the Applicant has not proposed similar language for Kyleena at this point.

8.7 SAFETY UPDATE

A 120-day Safety Update Report was submitted on March 16, 2016, covering the period from July 16, 2015 through January 15, 2016. The safety update included information about the two ongoing LCS12 clinical trials that are discussed further in Section 8.8.2 and information from the PBRER/PSUR covering the period from December 24, 2014 to December 23, 2015.

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.

8.8 Special Issues Relative to this NDA

8.8.1 EU Marketing Application

Kyleena has also been submitted for marketing approval to the European Union (b) (4) [redacted]

8.8.2 (b) (4) inserter

The to-be-marketed inserter has been evaluated in three studies, Protocols 13362, 13363 and 14371, all of which used LCS12 (Skyla). All studies had been completed by the time of the Four-Month Safety Update.

Protocol 13362 (Profiling 1 Study) began in January 2011 and was conducted in the US, Austria, Belgium and Germany, to assess user satisfaction with LCS12 vs. Yasmin. A total of 282 subjects were randomized to LCS12 and 279 had insertions. A total of 634 women-years (WY) of exposure were accrued in the three-year study, including an 18-month extension to the study. 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). The overall success rate for insertions was 98.9%.

No partial or total perforations and no total expulsions were reported. One subject was found to have an intrauterine, but displaced, LCS about a year post-insertion. Another subject had a partial expulsion (defined as LCS visible in the vagina or in the cervical canal) noted about two years into the study. A single case of endometritis was reported two weeks after insertion.

There were no deaths in this study; 22 SAEs were reported, four of which were considered treatment-related by the Applicant. The related SAEs per the Applicant were two ectopic pregnancies treated with laparoscopic salpingectomy, a hemorrhagic ovarian cyst and spontaneous abortion of a pregnancy of unknown location. Four pregnancies occurred, three of which were ectopic and one of which was the spontaneous abortion of a pregnancy of unknown location. The three ectopic pregnancies were managed laparoscopically.

Team Leader Comment:
The listing of the SAEs includes an abdominal pregnancy (Subject # 440010012) that was not considered drug-related. There is no narrative for this subject in the pregnancy or SAE listings. However, it is likely that such an ectopic pregnancy should be considered drug-related.

Protocol 13363 (Profiling 2 Study) began in September 2011 and was 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 382 had an insertion or insertion attempt. Three women discontinued prior to insertion of the LCS. Nulliparous women made up 76% of the study population. A total of 346 WY of exposure were accrued in the 12-month study.

Seven women (1.8%) had a failed initial insertion; of these, three 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 [two subjects], 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). The overall success rate for insertions was 97.9%.

No partial or total perforations were reported. Three women had partial expulsions of the LCS, two within a month of insertion and one about eight months post-insertion; there were no complete expulsions. There was one case each of salpingitis (four months post-insertion) and of endometritis (10 months post-insertion).

One death, a suicide in Subject # 360030028, was reported during this study, in a 26 y/o subject with a history of compulsive disorder treated with Effexor who had used LCS12 for five months at the time of death. No further information was provided in the narrative; the Applicant considered this death unrelated to study drug. Nine SAEs were reported, with one ectopic pregnancy and one chemical pregnancy as the only ones considered related by the Applicant. There were three pregnancies: the ectopic pregnancy, which resolved spontaneously, one electively terminated and one "chemical" pregnancy that spontaneously aborted.

Team Leader Comment:

As noted for the suicide in the phase 3 study, I consider the suicide in Study 13363 to be at least possibly drug-related. I concur otherwise with the Applicant's assessment of drug-relatedness.

Protocol 14371 (Adolescent Study) also began in September 2011 and was conducted in Austria, Belgium, Denmark, Finland, Germany, the Netherlands, Norway and Sweden. It was 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 304 subjects (302 < 18 years), 98% of whom were nulliparous. All subjects had an insertion or attempted insertion. A total of 275 WY of exposure were accrued in the 12-month study.

Seven women (2.3%) had a failed insertion. Six underwent a second attempt, all of which were successful. Reasons for initial failure were mainly inserter-related (IUS came out immediately after insertion [two subjects], IUS descended from fundus while removing inserter, thread stuck to scissors, IUS dislocated), while one subject was reported as "cervix was too tight." The overall success rate for insertions was 97.7%.

No partial or total perforations were reported. Nine women had partial expulsions, within 1-7 months of insertion, and one woman had a total expulsion within a month. Three cases of endometritis were reported; occurrence ranged from 3-5 days to four months after insertion.

One death was reported in this study, a woman who was a passenger in a motor vehicle collision. There were 23 SAEs reported, with three considered related by the Applicant (endometritis, and two cases of pelvic pain). No on-treatment pregnancies were reported.

Team Leader Comment:

In addition to SAEs the Applicant found possibly drug-related, I think the following should be considered SARs:

- **Ovarian torsion – this subject (# 300010007) experienced severe abdominal pain three months post-insertion; diagnostic laparoscopy found a torsed left ovary, which was treated by cystectomy. The cyst was described as 6 cm. The narrative notes that the investigator did not consider it drug-related but that the Sponsor did; however, it was not counted among the drug-related SAEs in the study report.**
- **Ovarian cyst – this subject (# 440030017) was hospitalized for abdominal pain and found to have a 4 cm ovarian cyst 10 months post-insertion. She was reported to have been treated medically, and ultrasound three days later found the cyst absent. Again, the narrative notes that the investigator did not consider it drug-related but that the Sponsor did; however, it was not counted among the drug-related SAEs in the study report.**

Pooled data:

I compared 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 were three partial perforations in Study A52238 vs. none in the three trials; rates of partial and total expulsion were 3.7% (Study A52238) vs. 1.4% (three studies). The PID rate in Study A52238 was 0.6%, the same as that in the three studies. Although the study duration was longer in the phase 3 study compared to the (b) (4) studies, most of these AEs occurred relatively early after insertion.

The healthcare provider assessment of ease of insertion was provided in two of the studies; the same two studies also asked subjects to assess the pain associated with insertion. Results from the pooled data are shown in Table 18.

Table 18 Assessments of Insertion Ease/Pain – Studies 13362 & 14371

Healthcare provider's assessment of ease of insertion (%)	
Easy	91.6
Slightly difficult	7.7
Very difficult	0.7
Subject's assessment of pain of insertion (%)	
None	19.1
Mild	39.3
Moderate	31.6
Severe	10.0

Source: Based on Summary of Clinical Safety, pp 206-7

Based on the pooled data for the three studies, the total rate of successful insertions was 98.2%, with 98.2% (948/965) of initial attempts succeeding, and 92.3% (12/13) of second attempts succeeding. For the single subject who had two failed attempts, the healthcare provider was unable to pass the IUS through her internal os.

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 with an overall insertion failure rate of 3.9% (3.9% failed first insertions, 3.3% failed second insertions).**
- **The data from the three LCS12 studies do not indicate any safety concerns with the use of the (b) (4) inserter.**
- **In addition to the clinical studies, the Applicant also provided bench/*in vitro* testing of the (b) (4) inserter, which was reviewed by CDRH.**
- **Finally, per the CDRH Compliance review, through July 2015, over (b) (4) units of Mirena and (b) (4) units of Skyla with the (b) (4) inserter have been sold.**

8.9 OVERALL ASSESSMENT OF SAFETY FINDINGS

The clinical safety database for LCS16 based on the phase 2 and 3 studies included 1,697 subjects who provided about 68,000 28-day cycles of exposure; over 24,000 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 LCS16 product. The Applicant provided the number of cycles the Division had requested, overall and in North American subjects.

There were two deaths in these clinical trials, one related to a motor vehicle crash, and a suicide, which is potentially associated with treatment, given the known association of progestins and depression. A second suicide occurred in the adolescent study of LCS12 and the (b) (4) inserter. However, overall, the risk of suicide attempts does not appear to be outside the background rate. SAEs occurred in about 6% of women, and I consider that 37 women (2.2%) had SAEs that were at least possibly drug-related. The most common were related to ectopic pregnancies, PID, abdominal pain, ovarian cysts, depressive disorders, spontaneous abortions and uterine perforation. The most common AEs that were associated with premature discontinuation (> 2%) were menstrual bleeding disorders, IUS expulsion, pelvic pain, and acne. Common AEs (5%) included vulvovaginitis, ovarian cysts, headaches, acne, abdominal pain, breast pain, dysmenorrhea, pelvic pain, and excessive and irregular bleeding. 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 IUSs, Mirena and Skyla.

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 were more frequent in nulliparae. AEs also occurred slightly more frequently in nulliparous women, particularly acne, dysmenorrhea, and pelvic pain. The risk of ectopic pregnancy appeared somewhat higher for nulliparae but the confidence intervals around the point estimates for the two groups overlapped and the absolute risk was very low (<0.3% over five years). Most of the few cases of PID and of endometritis occurred in parous women.

Overall, the safety profile of the LCS16 appears acceptable to support approval for prevention of pregnancy for up to five 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 contraceptive product very similar to currently marketed products.

10. Pediatrics

This application did not trigger the Pediatric Research Equity Act because it did not propose a new active ingredient, indication, dosage form, dosing regimen or route of administration.

11. Other Relevant Regulatory Issues

The Applicant certified that it did not use any debarred investigators. The Applicant submitted financial disclosure information for the full five-year period of Study A52238 plus one year post-study (financial information for phase 2 Study A46796 was submitted in the Skyla NDA), and provided due diligence information for those on whom financial disclosure information was missing. Two investigators for Study A52238 had disclosures:

- Dr. (b) (6) (Site (b) (6)) reported having received almost $192,000 in honoraria from the Applicant for the period of January 2008 through October 2011, a time during which the study was underway. Dr. (b) (6) enrolled (b) (6) subjects, of whom (b) (6) completed treatment (b) (6) of whom continued in the extension phase, with (b) (6) completing). (b) (6) of his subjects transferred to another site during the study.
- Dr. (b) (6) (Site (b) (6)) reported having received about $374,000 in honoraria from the Applicant for the same time period, during which the study was underway. Dr. (b) (6) enrolled (b) (6) subjects, of whom (b) (6) completed treatment, with none continuing into the extension phase. However, (b) (6) additional subjects transferred from another site to Dr. (b) (6) site during the study.

  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 each of these sites (< (b) (6)% 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, Ronald Ackerman at Site 2415 from participating in the extension phase of Study A52238 due to compliance problems. 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 of AEs. Site personnel were retrained; however, a follow-up audit in 2010 revealed lack of corrective actions undertaken. While the Applicant barred Dr. Ackerman from the extension phase, it allowed his site to complete the three-year phase of the study because it had completed all Year 2.5 visits at the time of the decision; at that time, 18 subjects were enrolled, 10 of whom had received LCS16. No pregnancies were reported at this site.

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. (Subsequently, the Office of Scientific Investigation (OSI) confirmed that he had not been permanently disqualified.) His site for Study A52238 enrolled six subjects, four of whom received LCS16. No pregnancies were reported at this site; all four LCS16 subjects discontinued prematurely due to AEs (two due to uterine cramping, one to acne and one to cervical dysplasia).

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.

OSI inspected three sites for Study A52238. The sites were chosen based on considerations that included the number of subjects enrolled and high discontinuation rates. One site (2411 [Jeffrey Baker] was in the US and two were foreign: (1501 [Maria Jose Miranda in Chile] and 1806 [Tamas Nyirady in Hungary]).

Dr. Baker's site (2411) enrolled 97 subjects, with 35 completing the study. He received a Voluntary Action Indicated (VAI) evaluation following review of 23 subjects' records, which indicated a number of documentation discrepancies in subject records. Specific concerns included unspecified changes to concomitant medications or adverse events, and discrepancies relating to potential use of back-up contraception by Subjects #241140, 241197 and 246201. Additional issues identified included enrollment of a few women who met exclusion criteria, minor discrepancies in AE reporting, and numerous out-of-window visits, resulting in IUS placement outside of the 7-day window from the onset of menses. Dr. Baker responded to the VAI notification and attributed the performance to a research coordinator who was terminated. He has instituted corrective actions and additional training for his team.

The OSI review concluded the following for this site:

> *The inspection revealed numerous examples of inadequate study documentation. Discrepancies between subject diaries and other source documentation were not readily explained. Of potential safety concern was the enrollment of subjects meeting exclusion criteria and the placement of IUDs in subjects outside the protocol-specified time window although no adverse outcomes appear to have resulted from the protocol deviation. Because the number and scope of deficiencies noted are of potential concern, the review division may wish to assess their impact on the evaluation of safety and efficacy. Otherwise, this study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.*

Team Leader Comment:

The observations relating to entry criteria, AE reporting and protocol adherence are unlikely to impact the safety and efficacy findings of the overall trial significantly. However, the discrepancies relating to possible use of back-up contraception are of concern, and an information request was submitted to the Applicant on August 17, 2016. The Applicant's response of August 24, 2016 indicated that scanning of the source data had resulted in "downshifting" of certain data elements (including use of

back-up contraception) from their original recording in the subject diaries. Because the scanned copies of the diaries were retained at the site, it is possible that site copies may be discrepant from the original source records. However, the original records were used in construction of the database, so use of back-up contraception was captured accurately and any cycles in which back-up contraception was used were appropriately excluded.

Based on this response, I concur that data from Dr. Baker's may be used in support of the NDA.

Dr. Miranda's site (1501) enrolled 56 subjects, with 34 completing the 3-year study (10 of the 17 who entered the two-year extension phase completed). He received a classification of No Action Indicated (NAI), following review of 18 subjects' records. The study appeared to have been conducted adequately and the data appear acceptable.

Dr. Nyirady's site (1806) enrolled 82 subjects, with 50 completing the 3-year study (18 of the 23 who entered the two-year extension phase completed). He received a NAI evaluation, following review of 27 subjects' records. The study appeared to have been conducted adequately and the data appear acceptable.

Roy Blay, Ph.D., from OSI made the following overall assessment and general recommendations in his review dated August 15, 2016:

The clinical sites of Drs. Baker, Miranda, and Nyirady were inspected in support of this NDA and the final classification of these inspections was Voluntary Action Indicated (VAI) for the inspection of Dr. Baker and No Action Indicated (NAI) for the inspections of Drs. Miranda and Nyirady.

Based on the results of the clinical investigator inspections, the study appears to have been conducted adequately, and the data generated by these sites appear acceptable in support of the respective indication.

12. Labeling

The Applicant submitted the proposed proprietary name Kyleena, which was found to be acceptable by DMEPA on February 17, 2016.

Carton and container labeling was reviewed and found acceptable by DMEPA, the Office of Prescription Drug Promotion (OPDP) and the CMC reviewer. The Applicant also submitted a "patient booklet cover" containing a consent form and follow-up reminder card); however, this was not reviewed, as it does not constitute FDA-approved labeling.

The label was submitted in the format prescribed by the Physician Labeling Rule (PLR); labeling for similar products (Mirena, Skyla and Liletta) is already in PLR format. The package insert and patient labeling were reviewed by DMEPA, 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 reminder card, which is not FDA-approved labeling. Labeling relevant to the Pregnancy and Lactation Labeling Rule was reviewed by Jeanine Best of the Labeling Development Team, Office of New Drugs.

During review of the Skyla NDA, the Division had agreed to 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. Specific issues discussed during labeling discussions for this NDA included use of "IUD" as a general term in labeling (the Applicant considers the LNG IUSs to be a subset of the term IUD), and use of the rate of uterine perforations based on pooled data for both LCS12 and LCS16, given that the two LCSs have the same dimensions and used the same inserter. 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. In addition, the AE frequencies proposed by the Applicant for labeling were based on a search strategy that avoids double-counting of subjects that may have had more than one similar preferred term coded for their AE. For that reason, labeling rates may vary slightly from the rates described in this review. Agreement on labeling was reached on September 16, 2016.

13. Recommendations/Risk Benefit Assessment

13.1 Recommended Regulatory Action

I recommend that LCS16 (Kyleena) receive an Approval action.

13.2 Risk Benefit Assessment

The efficacy of Kyleena in prevention of pregnancy is acceptable throughout the requested five-year treatment duration. Efficacy was very similar regardless of parity.

The risks associated with this IUS are those well-characterized in association with hormonal IUSs, and the safety data do not suggest that these risks are higher for this IUS, which is smaller and contains a lower LNG dose than the approved five-year LCS Mirena. 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 Kyleena is used in women without regard to parity. Safety data obtained from 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 discussed in Section 8.6, based on results from a large prospective non-interventional cohort study (EURAS-IUD) to evaluate the risks of Mirena and copper IUDs in new users,

(b) (4)

I believe that no further postmarketing requirements, commitments or postmarketing risk management activities are needed.

13.4 Recommendation for other Postmarketing Study Requirements and Commitments

I do not recommend that any postmarketing studies be required, (b) (4)

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
09/16/2016

HYLTON V JOFFE
09/16/2016
See the Division Director Memorandum.