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APPLICATION NUMBER:

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MEDICAL REVIEW(S)

CLINICAL REVIEW

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Reviewer Name(s)	Ronald J. Orleans, M.D.
Review Completion Date	December 26, 2012
Established Name	Levonorgestrel-releasing intrauterine system
(Proposed) Trade Name	Skylla®
Therapeutic Class	Progestin-containing intrauterine device
Applicant	Bayer HealthCare Pharmaceuticals Inc.
Formulation(s)	Intrauterine device
Dosing Regimen	Insertion into the uterine cavity (3 year contraceptive efficacy)
Indication(s)	Contraception
Intended Population(s)	Women of childbearing age

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Based on the data submitted in Bayer HealthCare Pharmaceutical's (the Applicant's) NDA submission, I recommend that NDA 203159 be approved for the indication of prevention of pregnancy for up to 3 years. This recommendation is based on the Applicant having demonstrated an acceptable Pearl Index (PI) and an acceptable safety profile for this product.

1.2 Risk Benefit Assessment

The PI for Skyla (hereafter referred to as LCS12) was derived from the data obtained from the phase 3 clinical trial A52238 (performed in Europe, North America and South America) which included women 18 to 35 years of age in whom an LCS12 insertion was at least attempted. Cycles in which back-up contraception was used were excluded from the analysis unless a pregnancy occurred in that cycle. The PI for Year 1 was calculated based on 5 pregnancies occurring over 15,763 28-day cycle equivalents. Based on these data, the PI of LCS12 for Year 1 is 0.41 (0.13, 0.96). The cumulative 3-Year PI was calculated based on 10 pregnancies occurring over 39,368 28-day cycle equivalents and was calculated to be 0.33 (0.16, 0.60). The cumulative pregnancy rate estimated by the Kaplan-Meier method per 100 women at the end of the first year is 0.39 (0.16, 0.94) and the cumulative pregnancy rate at the end of three years is 0.89 (0.5, 1.7). The PIs and Kaplan-Meier calculations provide sufficient evidence to support the efficacy of LCS12 for women who desire intrauterine contraception for up to 3 years.

The bulk of the LCS12 safety database is derived from a pooled analysis of data from Study A52238 and the comparative phase 2 Study A46796, which was performed in Europe. The safety assessment for LCS12 was based on the Full Analysis Set (FAS), which was defined as all women who were enrolled and had an LCS insertion attempt. A total of 1672 women, including 1,383 exposed for one year and 993 who completed the 3-year study, were assigned to the LCS12 FAS cohort. The population was generally healthy 18 to 40-year old females, predominantly Caucasian, and requesting intrauterine contraception.

The adverse events profile of LCS12 did not give rise to any new safety concerns. There were no unusual safety signals observed with regard to IUS-related events such as complications associated with insertions, removals, expulsions or perforations. A review of laboratory tests, vital signs, bone mineral density and other safety parameters that were measured also did not reveal any specific concerns.

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There were 2 issues in this review that required special attention. The first issue was the risk of ectopic pregnancy with this product. A total of 4 ectopic pregnancies in 1672 subjects occurred during treatment with LCS12 (pooled data), which resulted in an overall 3-Year risk of 0.2%. This risk of an ectopic pregnancy in this product is very low and is similar to the 0.1% risk with Mirena. A subanalysis by subject parity revealed the incidence rate in nulliparous subjects was 2 out of 608 or 0.3%, with a 1-year PI for ectopic pregnancy of 0.20 and a 3-Year PI of 0.17. In parous subjects, the incidence rate was 2 out of 1064 subjects or 0.2%, with a 1-Year PI of 0.11 and a 3-Year PI of 0.08. The confidence intervals of the calculated PIs overlap, so no conclusions can be made regarding relative risks relating to parity.

The second issue was the new (b) (4) inserter," which was not used in the 2 clinical trials. The inserter used in phase 2 and 3 studies (b) (4). This inserter was subsequently modified (b) (4). The insertion procedure itself remained unchanged.

In order to fully evaluate the safety and efficacy of the new inserter, the Division requested additional data from 3 ongoing phase 3 trials utilizing this new inserter. This request resulted in a Major Amendment and a 3-month extension of the goal date. A review of the submitted data was sufficient to conclude that there was no apparent increase in inserter-related complications such as failed insertions, expulsions or perforations in the 3 ongoing trials when compared to the pooled data from the 2 primary trials.

This reviewer concludes that based on the data from the 2 phase 3 clinical trials submitted to this NDA and based on the additional data submitted as a Major Amendment, LCS12 has a positive risk benefit and that the data supports marketing approval.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None

1.4 Recommendations for Postmarket Requirements and Commitments

Based on the clinical trials data submitted to this NDA, standard post-marketing surveillance is recommended to further monitor the safety and efficacy of LCS12. In Europe, largely due to concerns of the risk of ectopic pregnancy in nulliparous patients, the EURAS-LCS12 study has been proposed to prospectively monitor IUS safety in European women. The objective of this study is to assess the risk of unintended pregnancy, as well as ectopic pregnancy and insertion difficulties, in new users of LCS12 compared with users of established IUDs.

This review is based primarily on data from the phase 2 and phase 3 clinical trials and from the additional information requested from the Applicant. In my opinion, these data do not necessarily warrant specific postmarketing commitments. The risk that a pregnancy is ectopic is elevated with the use of any IUS. This risk can be adequately communicated in the label. No other specific risk management steps are recommended.

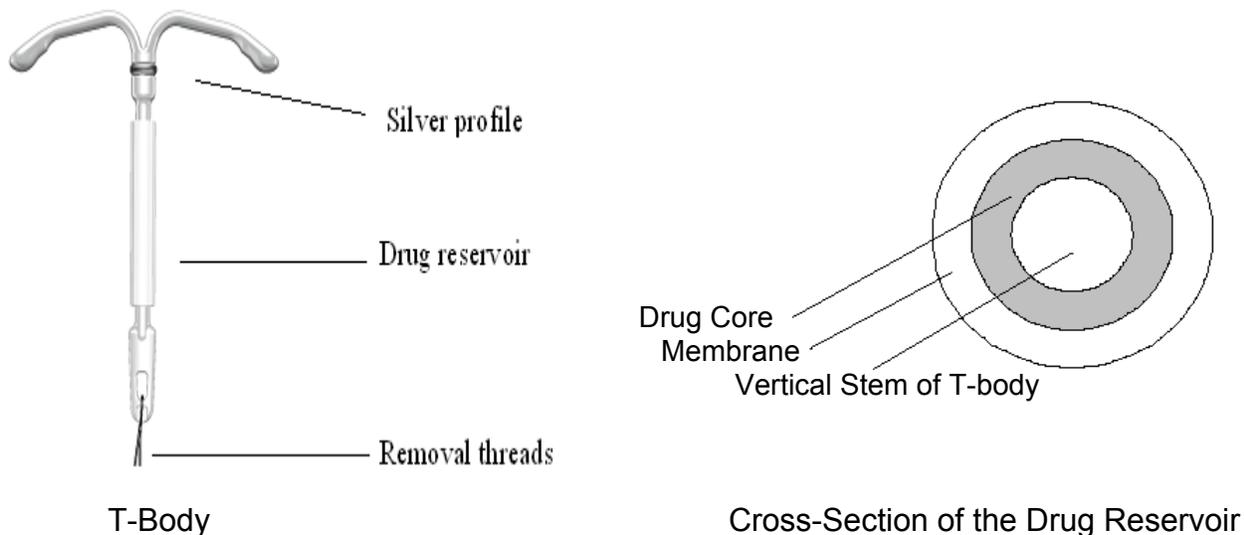
2 Introduction and Regulatory Background

2.1 Product Information

Bayer Pharmaceuticals Inc. (the Applicant) is seeking approval for a low-dose, levonorgestrel (LNG)-releasing intrauterine delivery system (IUS) for contraception. The proposed indication is the prevention of pregnancy for up to 3 years.

This LNG IUS (also referred to in study reports as LCS12) is composed of (1) the T-body (2) a drug core of 13.5 mg LNG, and (3) a covering outer membrane.

Figure 1 LCS12



The T-body consists of a vertical stem with two horizontal arms. There is a loop with attached polyethylene removal threads at one end of the vertical stem and the two horizontal arms are at the other end. A silver ring is added around the top of the vertical stem of the T-frame to facilitate detection during an ultrasound examination. Other excipients in the LCS12 include silica colloidal anhydrous and barium sulfate.

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The LNG reservoir is mounted on the vertical stem of the T-body. The drug reservoir consists of (b) (4) LNG covered with a polydimethylsiloxane membrane. (b) (4)

(b) (4) LCS12 has an *in vitro* LNG release rate of approximately 12 µg/24 hours (See Table 1).

A (b) (4) inserter adapted to the LCS dimensions was used in the phase 2 and 3 studies submitted to the NDA. However, for the ongoing phase 3b studies and for the proposed commercial product, a modified inserter (also referred to as the (b) (4) inserter) was developed (b) (4)

With the (b) (4) inserter, the removal threads are prefixed inside the shaft (b) (4)

The Applicant states that the actual insertion procedure remains unchanged.

The package containing the to-be-marketed LCS12 was also redesigned from that used in the phase 3 trial so that the LCS12 will be packaged in the correct horizontal position, (b) (4)

Medical Reviewer's Comments

- *Mirena®*, Bayer's marketed LNG-releasing IUS was approved under NDA 21-225 on December 6, 2000. It is the only approved LNG-IUS currently on the market and is currently marketed in more than 100 countries.
- Bayer is currently testing the modified (b) (4) inserter in several phase 3b clinical trials. This inserter has been approved for use with Mirena in 47 countries. Insertion data using the (b) (4) inserter are reviewed in Section 7.3.5.
- The structural frame material for the T- body that was used in the pivotal trial for this NDA is the same as the to-be-marketed product.
- LCS12 has not yet been approved in any country; however, marketing applications are being submitted outside the US in parallel with this NDA submission. Safety concerns raised by Sweden, a Reference Member State of the EU are discussed in Section 7.3.4.1.
- LCS12 has a lower daily release rate of LNG (12 µg vs. 20 µg) and a smaller insertion tube diameter than Mirena. Because of this smaller insertion tube, the Applicant believes that LCS12 will be easier to use in nulliparous patients than Mirena.
- The Applicant also believes that a lower daily dose of the progestin might be expected to reduce systemic exposure and progestin-related side effects.

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- *LCS12 is regulated as a drug product because it contains LNG. However, the T-body component of the LCS is treated as a device, necessitating a consultative review by CDRH.*

2.2 Tables of Currently Available Treatments for Proposed Indications

Currently, there are 2 FDA-approved IUSs available for intrauterine contraception. These are Mirena and the copper-containing ParaGard® T 380A.

Mirena was first approved for marketing in Finland in 1990 and has been approved in the US since 2000. It is currently approved for (1) intrauterine contraception for up to 5 years and (2) the treatment of heavy menstrual bleeding for women who choose intrauterine contraception as their method of contraception. The reported 12-month pregnancy rates for Mirena were less than or equal to 0.2 per 100 women (0.2%). The ParaGard® T 380A (NDA 018680) was originally approved in 1984. It is currently approved for intrauterine contraception for up to 10 years. The pregnancy rate in clinical studies of the ParaGard IUS has been less than 1 pregnancy per 100 women each year.

2.3 Availability of Proposed Active Ingredient in the United States

Levonorgestrel, the active drug component of LCS12, has a long history of use in combination with estrogen for gynecologic indications in the US. These indications include contraception (oral and intrauterine use), the treatment of heavy menstrual bleeding and the treatment of vasomotor symptoms due to menopause.

2.4 Important Safety Issues with Consideration to Related Drugs

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

- sexually transmitted infection and pelvic inflammatory disease with the subsequent risk of infertility
- uterine perforation or expulsion
- ectopic pregnancy
- pregnancy loss or septic abortion if a pregnancy occurs with an IUD in situ.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

LCS12 was studied under Bayer's IND 73,505.

Prior to submission of the IND, the Applicant requested a Type B Pre-IND Meeting to discuss the development program. This meeting was scheduled to take place on April 4, 2006; however, after reading the Division's draft comments, the Applicant determined

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that there were no further issues to be resolved and requested that the meeting be cancelled. The Division's final meeting minutes signed on May 1, 2006 included the following:

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

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

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

Several meetings and teleconferences have been held under this IND:

On June 22, 2009, the Division provided three recommendations regarding Study A52238:

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

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

A Type B End-of-Phase 2 Meeting was held on November 24, 2009 to discuss Clinical and Clinical Pharmacology topics. The following clinical comments were conveyed to the Applicant relating to the approval of LCS12 for the 3 year treatment duration:

- The Division requested that a minimum of 200 women complete the full 3 year treatment duration.
- The Division recommended that Bayer characterize the serum LNG pharmacokinetics after removal of the IUS.

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

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

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

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

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

- Bayer agreed to provide 28-day cycle information datasets as proposed by the Division and to describe the algorithm used to assign back-up contraception use to specific 28- day cycles in the Statistical Analysis Plan for the Integrated Analysis.

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

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

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

2.6 Other Relevant Background Information

2.6.1 Information Requests

As mentioned earlier in this review, a (b) (4) inserter adapted to the LCS dimensions was used in the phase 2 and 3 studies. However, for phase 3b studies and for the commercial product, a modified inserter (b) (4) inserter) was developed (b) (4). With this inserter, the removal threads are pre-fixed inside the shaft (b) (4).

In the 4-Month Safety Update Report, Bayer submitted data from ongoing Protocol 13362, which was the first study to utilize the (b) (4) inserter, and an interim analysis was provided to evaluate insertion-related information. The interim analysis was conducted after all LCS insertions and the associated 1 month follow up visits had been completed.

Medical Reviewer's Comments

- *A review of the interim analysis is found in Section 7.7.1 of this review.*
- *The data submitted by Bayer in the interim study report from Protocol 13362 related mainly to the assessment of the ease of insertion of the IUS but did not address whether intrauterine placement of the IUS is affected by the new*

inserter. The Division believed that the data obtained from the interim study report was therefore insufficient to support the safety and efficacy of the to-be-marketed product, which would contain this new relatively untested inserter.

- *Because of this insufficiency, on July 24, 2012, the Division requested the following information from Bayer:*
 - *All available data obtained subsequent to the 4-month Safety Update Reporting period ending January 31, 2012 regarding the to-be-marketed inserter. This would include any additional data from Protocol 13362 as well as new data, if available, from Protocols 13363 and 14371, both of which initiated enrollment in September, 2011. This information could be provided in the same format as presented in the interim study report A57046.*
 - *In addition, all available data regarding IUD-related complication rates using the new inserter, such as expulsions, perforations, endometritis, pelvic inflammatory disease, pregnancies and ectopic pregnancy should be submitted from all on-going studies. All collected data regarding the to-be-marketed IUS complications should be stratified by parity and all of the data should be compared to rates obtained in the primary study A52238.*
 - *Provide narrative summary data for study subjects in Study 13362 who underwent sonograms to verify appropriate intrauterine placement of the LCS. This should include (1) the criteria for "investigator discretion" to do a sonogram and (2) percentage of study subjects at these sites who had placement sonograms vs. those who did not.*
- *The above information was provided to the Division by Bayer on August 10, 2012. A review of this requested information can be found in Section 7.3.5.5*
- *This was considered to be a major amendment to the original application, which extended the PDUFA goal date from October 9, 2012 to January 9, 2013.*

2.6.2 Division of Medication Error Prevention and Analysis (DMEPA)

On October 2, 2011, the Division of Medication Error Prevention and Analysis (DMEPA) issued a letter communicating that Bayer's primary proposed proprietary name for LCS12, Skyla, was conditionally acceptable.

In their final review, DMEPA did not identify any vulnerabilities that could result in medication errors, so it had no objections to the proprietary name, Skyla.

2.6.3 Good Clinical Practice Assessment Branch, Office of Scientific Investigations

On March 6, 2012, the Division requested the Office of Scientific Investigations to audit 4 preselected sites from Study A52238 to insure data integrity. Two of these sites were

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in the US (Sites 2439 and 2403) and 2 were in Finland (Sites 1606 and 1609). Based on the review of preliminary inspection findings for these sites, the OSI reviewer stated in the Clinical Inspection Summary report dated August 10, 2012 that “the study data for Study A52238 (Protocol 310442) submitted by the Applicant appears reliable in support of NDA 203159.”

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

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

3.2 Compliance with Good Clinical Practices

The Applicant attests that the pivotal phase 3 clinical trial and the supportive phase 2 clinical trial were conducted in compliance with Good Clinical Practice.

However, during the course of this review, the following communications were received from Bayer.

On December 21, 2010 (IND 73505, S-0027) Bayer submitted an amendment to inform the Division of its decision to exclude one of the (US) Principal Investigators (Ronald Ackerman) in ongoing Protocol 310442 from participating in the extension phase of the study due to compliance problems at the site (Site 2415). The problems had to do with failure to follow the protocol, multiple protocol deviations related to study procedures and enrollment of ineligible subjects. Although excluded from the 2 year extension phase of the study, Bayer allowed this investigator to complete the 3 year phase of the study under intensive monitoring. A total of 56 subjects were screened at this site, 37 subjects were enrolled and 18 were assigned to the LCS12 group. No pregnancies were reported from this site.

On February 28, 2012, the Division received notification from Bayer (NDA 203159, S-0004) that another (US) Principal Investigator (Richard Muckerman II) for Protocol 310442 (Site 2434) was implicated in fraudulent behavior related to another sponsor's study. The Investigator's clinical research center, PPS Clinical Research, plead guilty to a federal felony charge related to obstruction of a 2010 FDA inspection. Site 2434 screened 7 subjects and enrolled 6 subjects of which 2 subjects were assigned to the LCS12 arm. No pregnancies were reported from this site.

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Medical Reviewer's Comment

- *Efficacy will be reported in Section 7 with and without data from the above two sites.*

3.3 Financial Disclosures

Bayer submitted a signed Certification: Financial Interests and Arrangements of Clinical Investigators form (Form FDA 3454) in compliance with 21 CFR part 54 for Studies A46796 (Protocol 308901) and A52238 (Protocol 310442). Bayer also provided a Financial/Certification Disclosure Table for each study.

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

For the phase 3 Study A52238, all the investigators/sub-investigators filed a Financial Certification/Disclosure form with the exception of two physicians:

- Anna-Mari Heikkinen, M.D. (Study Site 1606 in Finland) did not participate in the conduct of the study.
- Frederick Hodges, M.D. (Study Site 2441 in the U.S.) was never delegated any responsibilities in the study.

Only two physicians in Study A52238 marked "Yes" under Disclosable Information.

- (b) (6) was a principal investigator and coordinating investigator for Study A52238. (b) (6) is located at the (b) (6). The site recruited (b) (6) subjects or (b) (6) of the total population enrolled. Out of the (b) (6) subjects, (b) (6) were screen failures, (b) (6) entered treatment, (b) (6) dropped treatment, (b) (6) completed treatment, and (b) (6) are currently in treatment in the extension phase of the study. (b) (6) reported having received \$191,800.00 for honoraria from Bayer for research grants, promotional talks on both oral contraceptives and intrauterine products, and serving on advisory boards. These honoraria covered the period of January 2008 through October 2011.
- (b) (6) was also a principal investigator and coordinating investigator for study A52238. (b) (6) is located at the (b) (6). The site recruited (b) (6) subjects or (b) (6) of the total population enrolled. Out of the (b) (6) subjects, (b) (6) were screen failures, (b) (6) entered treatment, (b) (6) dropped treatment, and (b) (6) completed treatment. (b) (6) provided financial disclosure information and reported having received \$278,307.99 for honoraria from Bayer for research grants, promotional talks on both oral contraceptives and intrauterine products, and serving on advisory boards. These honoraria covered the period of January 2008 through October 2011.

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Medical Reviewer's Comment

- *The potential for [REDACTED] (b) (6) and [REDACTED] (b) (6) financial arrangements to bias the study finding is minimal as their sites recruited a total of 20 subjects or 0.69% of the total study population of 2885 subjects.*

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls (ONDQA)

The CMC reviewer for this application concluded the following:

- The applicant of this submission has not submitted sufficient information to assure the identity, strength, purity, and quality of the drug product.
- The Office of Compliance has not made an overall "Acceptable" recommendation for the facilities involved in this submission.
- Labeling issues have not been fully resolved.

Therefore, as of the August 6, 2012 date of the CMC review, this submission was not recommended for approval in its present form.

ONDQA/Biopharmaceutics

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

4.2 Clinical Microbiology

The Product Quality Microbiology Review was completed on March 26, 2012. From the product quality microbiology perspective, approval was recommended.

4.3 Preclinical Pharmacology/Toxicology

No preclinical pharmacology/toxicology studies were conducted with LCS12.

Medical Reviewer's Comment

- *In her review dated November 21, 2012, the Pharmacology/Toxicology reviewer stated that nonclinical data support approval of LCS12 for the prevention of pregnancy for up to 3 years.*

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

The mode of action of all non-hormonal IUDs occurs mainly in the endometrial cavity due to the general reaction of the endometrium to a foreign body, which produces an

environment that is spermicidal. This reaction consists of a sterile inflammatory response that produces tissue injury of a minor degree but sufficient enough to be spermicidal. Ovulation is generally not affected by non-hormonal IUDs.

The mode of action of LCS12 is mainly via its local progestogenic effects within the uterine cavity and cervix. The high LNG concentration in the endometrium causes thinning and atrophy, which inhibits implantation. These histological changes in the endometrium as well as a weak local foreign body reaction are observed with use of LCS12. In addition, LCS12 thickens the cervical mucus, creating a barrier to sperm penetration. Changes to the local milieu of the uterus and fallopian tubes inhibit sperm mobility and function, also preventing fertilization.

4.4.2 Pharmacodynamics

LCS12 has local progestogenic effects on the endometrium and the cervix. The local LNG levels stimulate histologic changes in the endometrium which include stromal pseudodecidualization and glandular atrophy. In the cervix, the mucus becomes scanty, thick and viscid. LNG released from the LCS12 system is also rapidly absorbed into the systemic circulation and affects ovulation frequency in some women.

Medical Reviewer's Comment

- *The serum LNG concentration during the 3 years of use of LCS12 did not suppress the hypothalamic-pituitary ovarian axis in the majority of women. In the primary clinical trial, evidence of ovulation was seen in 34 of 35 women in the first year and all 27 women in the third year.*

4.4.3 Pharmacokinetics

The pharmacokinetic (PK) characterization of LCS12 is based on data obtained from the phase 2 and phases 3 clinical studies. No clinical pharmacology studies were submitted to the NDA.

LCS12 was designed to have an initial *in vitro* LNG release rate of 12 µg/day. The *in vivo* release rate is approximately 10 µg/day in Weeks 3 to 4 and is reduced to approximately 5 µg/day after three years. The mean LNG *in vivo* release rate is approximately 6 µg/24 hours over the period of three years. Mirena, which is approved for up to 5 years of use, has an initial *in vitro* release rate is 20 µg of LNG daily, declining to 10 to 14 µg per day after five years.

Table 1 Pharmacokinetics of LCS12, LCS16 and Mirena

Parameter	LCS12 NDA 203159	LCS16	Mirena NDA 021225
Total LNG Content	13.5 mg	19.5 mg	52 mg
Dimensions Horizontal x vertical width of T-body (mm)	28 x 30	28 x 30	32 x 32
Insertion tube outer diameter (mm)	3.8	3.8	4.75
Drug Reservoir Diameter/Length (mm)	2.8/12	2.8/18	3.6/19
Initial <i>in vitro</i> LNG release rate	12 µg/day	16 µg/day	20 µg/day
Week 3-4 <i>in vivo</i> LNG release rate	10 ug/day	14.9 ug/day	-
Mean <i>in vivo</i> LNG release rate over 3 years	6.4 µg/day	9.6 µg/day	-
<i>In vivo</i> LNG release rate at the end of 3 years (LCS) and 5 years (Mirena)	4.8 ug/day	7.4 ug/day	15 ug/day

Source: Adapted from Clinical Study Report A52238, Page 17, Table 7-1

Medical Reviewer’s Comments

- The LCS12 and the LCS16 IUSs were smaller in dimensions (i.e., 28 x 30 mm) than Mirena (32 x 32 mm). Also, the insertion tube used for the LCSs was thinner (diameter 3.8 mm) than the one used to insert Mirena (4.75 mm).
- The main physical difference between the LCS12 and the LCS16 is (b) (4) (b) (6) This (b) (6) result in the different LNG release rates.
- The amount of LNG does not directly affect the initial release rate, but does affect the effective lifetime of the drug product.

5.1 Tables of Studies/Clinical Trials

NDA 203159 consists of one phase 3 primary clinical trial and one phase 2 supportive trial. All trials were conducted under IND 73,505.

The phase 3 primary clinical trial is Study A52238 (protocol 310442) is entitled “Multi-center, open-label, randomized study to assess the safety and contraceptive efficacy of two doses (*in vitro* 12 µg/24 h and 16 µg/24 h) of the ultra low dose levonorgestrel contraceptive intrauterine systems (LCS) for a maximum of 3 years in women 18 to 35 years of age and an extension phase of the 16 µg/24 h dose group (LCS16 arm) up to 5 years.” Study A52238 was conducted at sites in Europe, the US, Canada and South America between 2007 and 2011.

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Medical Reviewer's Comments

- *Based on earlier agreements with Bayer, the evaluation of LCS12's efficacy will be based on the 12-month and cumulative 3-year unadjusted PI for women 18 to 35 years of age from the FAS population of the phase 3 study only.*
- *Since LCS12 is the drug for which approval is sought, the LCS16 extension phase of the phase 3 study will not be addressed in this review.*

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

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Table 2 Completed Clinical Trials

Study Number/Protocol	Design	Study population	Number of women by treatment group	Main outcomes
Phase 3				
A52238/310442 -11 countries (Europe, US, Canada, South America) -138 study centers -August 20, 2007 to June 8, 2011	-3 year multicenter, randomized, open label, 2-arm, parallel group - 2 year extension for single-arm LCS16 only planned to end June, 2013	- Healthy -18 to 35 years -Nulliparous or parous women	Randomized=2885 FAS = 2884 <u>LCS12</u> -FAS = 1432 -Completed = 819 -Mean duration of treatment = 821 days or 2.25 WY <u>LCS16</u> -FAS = 1452 -Completed = 870 -Mean duration of treatment = 843 days or 2.31 WY	-Pregnancy rate -Bleeding pattern -Safety
Phase 2				
A46796/308901 -5 countries in Europe -37 study centers -April 19, 2005 to December 9, 2008	-Multicenter, randomized, open label, controlled, 3-arm, parallel group -3 years	-Healthy -21 to 40 years -Nulliparous or parous women	FAS = 741 <u>LCS12</u> -FAS = 240 -Mean duration of treatment = 915 days or 2.51 WY <u>LCS16</u> -FAS = 245 -Mean duration of treatment = 912 days or 2.50 WY <u>Mirena</u> -FAS = 256 -Mean duration of treatment = 895 days or 2.45 WY	-Pregnancy rate -Bleeding pattern -Safety

Source: Medical Reviewer

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Medical Reviewers Comment

- *The two studies have different inclusion criteria regarding age, i.e., 18 to 35 years in Study A52238 compared to 21 to 40 years in Study A46796.*

5.2 Review Strategy

The primary phase 3 clinical trial, A52238, as well as the supportive phase 2 clinical trial, A46796, were both reviewed to assess the safety and efficacy of LCS12. Efficacy was assessed primarily from the phase 3 trial. Safety was assessed using the pooled data from both studies.

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 Primary Clinical Trial (Study A52238, Protocol 310442)

5.3.1.1 Study Title

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

5.3.1.2 Study Objectives

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

5.3.1.3 Clinical Trial Design

This trial was a multicenter, multi-national, randomized, open-label study comparing the LNG-IUS with a second LNG-IUS containing a different LNG load. The trial was conducted at 138 study sites in 11 countries in Europe, Latin America, the US and Canada.

The women in the study were between 18 and 35 years of age, in good general health, and in need of contraception. A total of 3661 women were screened for participation in the study, leading to a total of 2885 women who were randomized. Both nulliparous and multiparous women were enrolled. The full analysis (FAS) cohort was used for all efficacy and safety analyses. The FAS was defined as including all women for whom the IUS was inserted or the insertion of an IUS was attempted. One subject was randomized to the LCS16 group but no insertion was attempted and so she was

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excluded from the FAS. A total of 1432 subjects were randomized to receive LCS12 and a total of 1452 women were randomized to the LCS16 cohort.

5.3.1.4 Clinical Trial Sites

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

Table 3 Countries, Study Sites, Enrollments, and Treatments

Countries	Study Sites	Enrollment	Treatment	Randomized	FAS ¹
USA	57	1543	Total	1104	1103
			LCS12	540	540
			LCS16	564	563
Finland	15	589	Total	526	526
			LCS12	265	265
			LCS16	261	261
Canada	13	235	Total	184	184
			LCS12	92	92
			LCS16	92	92
Sweden	11	219	Total	178	178
			LCS12	88	88
			LCS16	90	90
Netherlands	9	199	Total	170	170
			LCS12	87	87
			LCS16	83	83
Hungary	8	336	Total	303	303
			LCS12	154	154
			LCS16	149	149
France	8	47	Total	43	43
			LCS12	22	22
			LCS16	21	21
Norway	5	95	Total	79	79
			LCS12	38	38
			LCS16	41	41
Argentina	5	169	Total	137	137
			LCS12	65	65
			LCS16	72	72
Mexico	4	131	Total	85	85
			LCS12	43	43
			LCS16	42	42
Chile	3	98	Total	76	76
			LCS12	38	38
			LCS16	38	38

¹ Full Analysis defined as all women for whom the IUS was inserted or the insertion of an IUS was attempted.

Source: CSR, A52238, Page 69, Table 8-1

5.3.1.5 Inclusion Criteria

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

5.3.1.6 Exclusion Criteria

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

15. Concomitant use of other sex-hormone containing preparations or intrauterine devices.
16. Use of any long-acting injectable sex-hormone preparations within 12 months prior to start of study medication, and if entering subset 2 or subset 3: any sex-hormone administration within one month prior to start of the study medication.
17. If entering subset 2: any drug that might affect the blood coagulation (e.g., heparin, coumarin) within one month prior to start of the study medication.
18. If entering subset 2: any known condition that might affect the blood coagulation.
19. Established immunodeficiency.
20. Any known hypersensitivity to the constituents of the LCS.
21. Diagnosed or suspected malignant or premalignant disease at the screening.
22. Arterial hypertension not responding to treatment, with systolic pressure > 140 mm Hg or diastolic pressure > 90 mm Hg.
23. Current (or history of) severe hepatic diseases including benign or malignant tumors. There should be an interval of at least three months between the return of liver function values to normal and the start of study treatment (i.e., LCS insertion).
24. History of chronic alcoholism, drug dependence or abuse, psychotic states or severe neurosis or any other condition that, by judgment of the investigator, might impair subject's ability to cooperate.
25. Known or suspected HIV infection or high risk for sexually transmitted disease (STD).
26. Any clinically significant condition or laboratory result that, in the opinion of the investigator, compromises subject's safety, or might interfere with the evaluations or prevent the completion of the study. Non-inclusion laboratory values will be flagged by the laboratory based on predefined ranges.
27. Participated in another clinical study or consumed another experimental drug within one month prior to visit 1.
28. Previous participation in this study.
29. A person with close affiliation with the investigational site; e.g., close relative of the investigator, dependent person, employee or student of the investigational site.
30. Hungary only: Nulliparous

Medical Reviewer's Comment

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

5.3.1.7 Concomitant Therapy

Concomitant therapy was defined as either the continuation of a treatment started before the LCS insertion or addition of a new treatment during the study treatment period.

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All concomitant medications were reported on the CRF as follows: brand name of the medication, indication, dose, frequency, route of administration and start and stop dates.

When LCS removal was scheduled (at premature discontinuation/end of the study visit), the subject was to start using a condom or another barrier method of contraception at least 7 days before LCS removal, unless the removal was to take place during the first 7 days of menstruation.

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

Medical Reviewer's Comment

- *Backup contraception (e.g., condoms to prevent STD) was used by only a few women and over short periods of time. In Years 1-3 of the study, over 84% of subjects consistently used no backup contraception at all. Less than 1.0% of women used backup contraception for 5 months or more.*

5.3.1.8 Study Procedures

Scheduled Visits

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

Screening Visit (Visit 1):

Informed Consent was obtained.

Baseline Visit (Visit 2):

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

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Medical Reviewer's Comment

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

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

Interim Visits (Visits 3-9):

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

End of Study Visit (Visit 10):

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

Additional variables were studied in four subsets in preselected centers. Efficacy evaluations were conducted in subsets 1 and 2A, pharmacokinetics in subset 3 and safety in subsets 2B and 4. Subsets 2A and 2B were the same individuals.

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

5.3.1.9 Primary Efficacy Variables

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

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

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

Medical Reviewer's Comments

- *In both studies, A52238 and A46796, serum HCG test was replaced by the urine pregnancy test at the end of study visit so that the test result was available before the IUS removal. This was implemented by Amendment in both studies.*
- *In Study A52238, women performed home pregnancy tests as needed. The definition of "as needed" was not specifically defined in the protocol. In Study A46796, women were asked to perform pregnancy tests on a monthly basis and record the results in their bleeding diary.*

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

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

Unadjusted and adjusted PIs were calculated.

- The unadjusted PI included pregnancies that occurred during the exposure time ending with removal or partial or total expulsion of the LCS.

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- For the adjusted PI, only the exposure time until the IUD was last known to be in situ or displaced within the uterine cavity was considered.

Medical Reviewer's Comments

- *Pregnancies that occurred after partial expulsion but before the IUS was removed were counted in the unadjusted PIs but would not have been counted in the adjusted PI calculation. There were no cases like this in either of the two studies.*
- *To determine efficacy, this review will focus on the unadjusted Year 1 PI and the unadjusted cumulative 3-year PI.*

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

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

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

Medical Reviewer's Comments

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

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

5.3.1.10 Secondary Efficacy Variables

Bleeding

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

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

Medical Reviewer's Comment

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

The following definitions were used to describe the bleeding.

Table 4 Bleeding/Spotting Definitions

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

Source: CSR A52238, Page 57, Table 7-6

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PK Analysis (Subset 3)

The PK analysis set consisted of a total of 24 subjects (12 in each treatment group) who completed the 3-year study and provided a 3-year LNG and SHBG sample. A blood sample for the determination of serum LNG and SHBG was collected one sample per subject at one of the Visits 3 through 10.

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

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

Ovarian and Cervical Function (Subset 1)

Ovarian function was studied by determining serum concentrations of progesterone, and estradiol in a total of 40 subjects (20 per treatment arm).

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

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

Endometrial Histology (Subset 2A)

Endometrial histology was studied in a total of 60 subjects (30 per treatment arm) on a yearly basis. Specimens were examined by a blinded pathologist at baseline, and after 1, 2, and 3 years of treatment.

5.3.1.11 Safety Data

The following safety parameters were monitored during the clinical trial:

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- Adverse events (AEs), serious AEs (SAEs) presented using MedDRA (version 14.0)
- Concomitant medications
- The occurrence of dysmenorrhea
- Ease of LCS insertion and removal by the investigator
- LCS insertion/removal ease and pain by the subject
- The IUS expulsion and perforation rates
- The overall discontinuation rates
- Ectopic pregnancies
- The occurrence of pelvic inflammatory disease (PID)
- The occurrence of ovarian cysts (these were reported as AEs if they were abnormal non-functional cysts and/or had a diameter > 3 cm)
- Vital signs
- Physical and pelvic examinations, including vaginal and cervical smears and vaginal ultrasound
- Clinical laboratory tests
- Endometrial safety (subset only)
- Bone mineral density (subset only)

5.3.1.12 Protocol Amendments

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

Amendment 1

Amendment 1 dated October 4, 2007 specified the following:

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

Amendment 2

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

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

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Prior to implementation of this amendment, a total of 3051 subjects had been screened and 2125 subjects had been randomized for this study. Of these, a total of 1175 subjects had been screened and 614 subjects had been randomized in the USA and Canada.

Amendment 3

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

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

Amendment 4

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

Amendment 5

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

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

5.3.1.13 Protocol Deviations

A total of 7920 protocol deviations were recorded for 2421/2884 women (83.9%). More women in the LCS12 group than in the LCS16 group had deviations (87.9% vs. 80.0%).

Protocol deviations in 61 women (LCS12: 39 [2.7%], LCS16: 22 [1.5%]), were assessed as major but did not lead to exclusion from the analyses.

The major protocol deviations were nearly all due to use of excluded concomitant medications except for Subject 160710, who was found to be participating in another clinical trial.

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Table 5 gives an overview of all protocol deviations. The majority of deviations were procedure deviations (68.3%; e.g., individual examinations not done, condom not used prior to removal of IUS) or time-schedule deviations (50.5%; e.g., visits a few days early or late).

Treatment deviations consisted mostly of the LCS not being inserted during the first 7 days of menstruation. Inclusion or exclusion errors consisted of e.g., delivery or abortion less than 6 weeks before Visit 1, irregular menstrual cycle, history of PID, Pap result not available.

Randomization errors included insertion of the wrong dose LCS.

Table 5 Subjects (%) with at least one protocol deviation, FAS

	LCS12 N=1432 (100%)	LCS16 N=1452 (100%)	Total N=2884 (100%)
At Least One Minor Protocol Deviation:	1259 (87.9%)	1162 (80.0%)	2421 (83.9%)
-Inclusion/exclusion error at study entry	56 (3.9%)	60 (4.1%)	116 (4.0%)
-Randomization/ registration error	10 (0.7%)	7 (0.5%)	17 (0.6%)
-Withdrawal criteria present but not withdrawn	4 (0.3%)	3 (0.2%)	7 (0.2%)
-Excluded concomitant treatment	20 (1.4%)	13 (0.9%)	33 (1.1%)
-Treatment deviation	59 (4.1%)	71 (4.9%)	130 (4.5%)
-Time schedule deviation	716 (50.0%)	741 (51.0%)	1457 (50.5%)
-Procedure deviation	1088 (76%)	883 (60.8%)	1971 (68.3%)
At Least One Major Protocol Deviation	39 (2.7%)	22 (1.5%)	61 (2.1%)
-Inclusion/exclusion error at study entry	2 (0.1%)	1 (<0.1%)	3 (0.1%)
-Excluded concomitant treatment	38 (2.7%)	22 (1.5%)	60 (2.1%)

Source: CSR A52238, Page 74, Table 8-5 and Page 61 of 1253, Table 14.1.1/11

Medical Reviewer's Comments

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

5.3.2 Supportive Clinical Trial (Study A46796, Protocol 308901)

5.3.2.1 Study Title

Study A46796 is entitled: "Multi-center, open, randomized, dose finding phase II study to investigate for a maximum of three years ultra low dose levonorgestrel contraceptive

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intrauterine systems (LCS) releasing *in vitro* 12 µg/24 h and 16 µg/24 h of levonorgestrel compared to MIRENA in nulliparous and parous women in need of contraception.”

The study was performed at 37 centers located in Finland, Hungary, Norway, Sweden, and the United Kingdom and enrolled parous and nulliparous women, ages 21 to 40 years who needed contraception.

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

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

The study was conducted according to the final approved protocol, dated March 4, 2005 and its amendments 1 (dated November 24, 2005) and 2 (dated December 13, 2007). The study was conducted from April 19, 2005 to December 9, 2008.

Medical Reviewer's Comments

- *There were some differences between the phase 2 and phase 3 studies in population and study design:*
 - *The women in Study A52238 were slightly younger (inclusion age 18 to 35 years) than those in Study A46796 (inclusion age 21 to 40 years, actual age range: 20 to 41) and came from a broader geographic population (Europe, US, Canada, South America) than those in Study A46796 (Europe only).*
 - *Study A52238 had a much larger population (2884 women) than Study A46796 (741 women). In the pooled LCS groups, 85.6% of women were from Study A52238 (LCS12, 1432/1672; LCS16, 1452/1697). Therefore, the pooled analysis of the LCS groups is driven mainly by Study A52238.*
 - *Study A52238 included a higher proportion of nulliparous women than Study A46796 (39.2% vs. 21.5%).*
 - *In Study A46796, specific side effects classified as progestin-related (acne, bloating, breast pain, breast tension, edema, headache, mood changes, nausea and weight gain) were assessed at every visit via specific questioning. In contrast, these events were recorded as reported voluntarily by the women in Study A52238. This difference in AE reporting*

may have led to a higher frequency of certain progestin-related side effects in Study A46796 than in Study A52238.

5.3.2.2 Study Objectives

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

5.3.2.3 Clinical Trial Design

A total of 905 women between 21 and 41 years of age were screened, leading to a total of 742 who were randomized in a ratio of 1:1:1 and 738 who had an IUS inserted (LCS12: 239, LCS16: 245, Mirena: 254). All of the 738 women treated were included in the FAS, which was used for the efficacy and safety analyses. There were no major protocol deviations. A total of 208 women (28.2%) discontinued the study prematurely.

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

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

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

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

The subsets were the following:

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

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5.3.2.4 Clinical Trial Sites

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

5.3.2.5 Inclusion Criteria

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

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

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

Medical Reviewer's Comments

- *The age limit for study inclusion was higher than in the pivotal study A52238 (18 to 35 years inclusive). Otherwise, the inclusion and exclusion criteria were very similar in both studies.*
- *Although the inclusion criterion stated subjects must be between 21 to 40 years of age to be enrolled, the actual ages of enrolled study subjects were 20 to 41.*
- *Inclusion criteria included an ultrasound result indicating that the dimensions of the uterine cavity were suitable (investigators' discretion) for placement of an LNG-IUS of maximum dimensions 32 mm X 32 mm (Mirena).*

5.3.2.6 Exclusion Criteria

1. Known or suspected pregnancy or lactation.
2. End of last pregnancy; vaginal or cesarean delivery less than 12 weeks, or abortion within 12 weeks immediately before screening.
3. History of ectopic pregnancies.
4. Infected abortion or postpartum endometritis during the past 3 months.
5. Abnormal uterine bleeding of unknown origin.

6. Any genital infection (until successfully treated).
7. Descriptive diagnoses of epithelial cell atypias (not benign atypias) or more serious disorder in cervical smear (according to the Bethesda System) at screening and not responding to treatment.
8. History of or current pelvic inflammatory disease.
9. Congenital or acquired uterine anomaly.
10. Any distortion of the uterine cavity (for example, by fibroids) likely to cause problems during insertion, retention or removal of the IUS, in the opinion of the investigator.
11. History of, diagnosed or suspected genital malignancy, and untreated cervical dysplasia.
12. Previous or current climacteric symptoms.
13. Current endometrial polyps.
14. Ovarian cysts with diameter >3 cm.
15. Concomitant use of intrauterine device.
16. Any long-acting injectable sex-hormone preparations within six months prior to start of study medication, and if entering subset 3, then oral, implanted, transdermal, intrauterine or intravaginal sex hormone administration within one month prior to IUS insertion.
17. Established immunodeficiency.
18. Any known hypersensitivity to the constituents of the IUS.
19. Diagnosed or suspected malignant or premalignant disease.
20. Arterial hypertension not responding to treatment with systolic pressure >160 mmHg or diastolic pressure >95 mmHg after 5 minutes resting measured in sitting position.
21. Liver diseases: Presence or history of severe hepatic diseases including benign or malignant tumors. There should be an interval of at least 3 months between the return of liver function values to normal and the start of study medication intake.
22. History of chronic alcoholism, drug dependence or abuse, psychotic states or severe neurosis or any other condition that by judgment of the investigators might impair subjects' ability to cooperate.
23. Known or suspected HIV infection or high risk for sexually transmitted disease (STD).
24. Any clinically significant condition or laboratory result that, in the opinion of investigator, compromise subject safety, might interfere with the evaluations or prevent the completion of the trial.
25. Participation in another clinical trial within 1 month or intake of an experimental drug within 3 months prior to screening.
26. Previous assignment to treatment (e.g., randomization) during this study.
27. Close affiliation with the investigational site; e.g., close relative of the

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investigator, dependent person (e.g., employee or student of the investigational site).

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

Medical Reviewer's Comments

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

5.3.2.7 Concomitant Therapy

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

5.3.2.8 Study Procedures

Scheduled Visits

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

Screening Visit (Visit 1):

Informed Consent was obtained.

Baseline Visit (Visit 2):

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

Interim Visits (Visits 3-8):

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

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

5.3.2.9 Primary Efficacy Variables

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

Medical Reviewer's Comment

- *There were 3 women (1 in the LCS12 and 2 in the Mirena group) for whom the insertion was not successful. The one subject in the LCS12 cohort who was not included in the FAS did not significantly affect the PI calculation for this supportive study.*

5.3.2.10 Secondary Efficacy Variables

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

Cumulative Failure Rates

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

Bleeding

Subjects completed vaginal bleeding diaries on a daily basis. Bleeding outcomes were reported as the number and length of episodes, with bleeding graded as "none," "spotting" (no need of sanitary protection, or panty liners only), "light" (need of sanitary protection yet less than menstruation), "normal," or "heavy" (more than normal menstruation according to the subjects' experience).

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PK Analysis (Subset 3)

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

Ovarian and Cervical Function (Subset 1)

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

Endometrial Histology (Subset 2)

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

Other Outcomes

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

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

5.3.2.11 Safety Data

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

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

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done by (b) (4), and histological samples (subset 2) were analyzed by (b) (4)

5.3.2.12 Protocol Amendments

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

Amendment 1

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

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

Amendment 2

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

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

5.3.2.13 Protocol Deviations

A total of 2080 protocol deviations were recorded for 597/738 women (80.9%). No protocol deviations were assessed as major and no deviations led to exclusion from the analyses. The majority of protocol deviations (57.9%) were procedure deviations; e.g., a condom was not used prior to removal of the IUS. The next most frequent (40.8%) were time schedule deviations; e.g., visits a few days early or late. and treatment deviations (29.9%); e.g., the IUS used for less than 35 or more than 38 months.

6 Review of Efficacy

Efficacy Summary

One phase 3 clinical trial and one phase 2 clinical trial have been submitted to the NDA

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to support the marketing claim of prevention of pregnancy for up to 3 years. The primary efficacy variable was the number of unintended pregnancies during treatment measured by the PI with 2-sided 95% confidence intervals (CI) and life-table analysis (Kaplan-Meier method). The PI was based on 28-day equivalent cycles and was defined as the number of pregnancies per 100 woman-years.

Proof of efficacy of LCS12 is based on data from the phase 3 clinical trial A52238. Based on the data from this study, the unadjusted PI of LCS12 for Year 1 is 0.41 (0.13, 0.96). The 3-Year unadjusted PI is 0.33 (0.16, 0.60). The cumulative pregnancy rate estimated by the Kaplan-Meier method per 100 women at the end of the first year is 0.39 (0.16, 0.94) and at the end of the third year is 0.89 (0.48, 1.66).

These PIs provide adequate evidence to support the efficacy of LCS12 in the population targeted for marketing.

Medical Reviewer's Comments

- *In comparison, the Medical Officer's review of Mirena completed in December, 2000 documented that the PI for Mirena at 1 year was 0.19 (0.02, 0.70) and at 5 years was 0.08 (0.02, 0.23). The cumulative 5-year pregnancy rate reported in the current product label for Mirena is 0.7 per 100 women.*
- *Although cross-study comparisons are difficult to make, it would appear that LCS12 is very close to Mirena regarding efficacy.*

6.1 Indication

The Applicant's proposed indication for LCS12 is the prevention of pregnancy for up to 3 years.

6.1.1 Methods

Primary Analysis

The primary efficacy analysis for the approval of LCS12 is based on Study A52238.

Medical Reviewer's Comment

- *By previous agreement with the Applicant, the Division required only one phase 3 clinical trial to obtain approval for this product. The contraceptive efficacy of LCS12 is therefore based on data obtained from the primary Study A52238. The smaller phase 2 Study A46796 is only viewed as supportive.*

In Study A52238, a total of 2885 women were randomized to treatment, and an attempt to insert an LCS device was made in 2884 of them. All randomized women in whom an insertion was at least attempted were analyzed and included in the FAS for this study.

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In Study A46796, a total of 742 women were randomized to treatment. Of these, 738 (99.5%) had an LNG-IUS successfully placed (LCS12: n=239/240; LCS16: n= 245/246; Mirena: n= 254/256). Only randomized women with a successful IUS insertion were included in the FAS.

Contraceptive efficacy was based on the number of pregnancies that occurred during treatment or for which the estimated date of conception was within 7 days after IUS removal or detection of expulsion. The primary efficacy endpoint was the PI. Supportive Kaplan-Meier estimates of the cumulative pregnancy rate were also calculated using total exposure time based on exposure days and based on 28-day cycles.

Secondary Analysis

In Studies A52238 and A46796, the secondary analysis was the cumulative failure rate calculated using the Kaplan-Meier method. Other secondary analyses were descriptive bleeding data, treatment compliance, return to fertility and user satisfaction.

6.1.2 Demographics

In Study A52238, 80.0% of women in the FAS were Caucasian. The mean age of the subjects was approximately 27 years with a range of 18-35 years. In both treatment groups, almost 40% of the subjects were 25 years of age or younger and 39.2% of women were nulliparous. At screening, 98.9% of women were sexually active.

The FAS cohort included 1287 North American women, of whom 632 received LCS12 and 655 received LCS16.

Table 6 Baseline Demographics, FAS, Study A52238

Variable	LCS12 N = 1432 (100%)	LCS16 N = 1452 (100%)	Total N = 2884 (100%)
Caucasian	1141 (79.7%)	1164 (80.2%)	2306 (80%)
Black	75 (5.2%)	74 (5.1%)	149 (5.2%)
Hispanic	165 (11.5%)	159 (11.0%)	324 (11.2%)
Asian	11 (0.8%)	17 (1.2%)	28 (1.0%)
Other	39 (2.7%)	38 (2.6%)	77 (2.7%)
North American women	632	655	1287 (44.6%)
Mean age in years (range)	27.2 (18-35)	27.1 (18-35)	27.1 (18-35)
Age ≤ 25 years	566 (39.5%)	564 (38.8%)	1130 (39.2%)
Age > 25 years ≤ 35 years	866 (60.5%)	888 (61.2%)	1754 (60.8%)
Mean weight (kg)	68.7	68.7	68.7
Mean height (m)	1.647	1.647	1.647
Mean body mass index (kg/m ²)	25.32	25.32	25.32
Nulliparous	556 (38.8%)	574 (39.5%)	1130 (39.2%)
One birth or more	876 (61.2%)	878 (60.5%)	1754 (60.8%)
Currently sexually active	1416 (98.9%)	1435 (98.8%)	2851 (98.9%)
Current smokers	334 (23.3%)	360 (24.8%)	694 (24.1%)
Uterine length (cm)	72.0	72.2	72.1
Mean # of births (range)	1.1 (0-6)	1.1 (0-6)	1.1 (0-6)
Mean # vaginal deliveries(range)	0.9 (0-6)	0.9 (0-5)	0.9 (0-6)
Mean # cesarean sections (range)	0.3 (0-3)	0.2 (0-3)	0.2 (0-3)
Mean # of ectopic pregnancies	0.0	0.0	0.0

Source: CSR A52238, Page 263, Table 14.1.1,

Medical Reviewer's Comments

- *The treatment groups were similar with respect to demographic and baseline characteristics and gynecological history.*
- *A total of 98.9% of women gave a history of regular menstrual cycles. Only 0.9% of women in the LCS12 group and 1.2% of women in the LCS16 group reported irregular cycles.*
- *The average cycle length in both LCS groups was 28 to 29 days.*
- *At the pre-IND meeting held April 4, 2006, the Division requested data for a minimum of 10,000 28-day equivalent cycles for the first year of use and that a*

total of 45% of these cycles should be from subjects in North America. This request was successfully met by the Applicant.

- *The FAS cohort for both groups included 1287 North American women. Of these, 632 women received LCS12 and 655 women received LCS16.*
- *Per region, the number of women included in the analysis in the LCS12 group was as follows: 654 from European countries, 632 from North America and 146 from Latin America.*

Supportive Study A46796 was done entirely in Europe with the following demographics.

Table 7 Baseline Demographics, FAS, Study A46796

Variable	LCS12 N=240 (100%)
Ethnic group	
• Caucasian	239 (99.6%)
• Hispanic	1 (0.4%)
Mean age (range)	32.2 yrs (21-41)
• 18 to 25 years	38 (15.8%)
• 26 to 35 years	116 (48.3%)
• > 35 years	86 (35.8%)
• 18 to 35 years	154 (64.2%)
Mean BMI (kg/m²)	24.05
• ≤ 30 kg/m ²	222 (92.5%)
• > 30 kg/m ²	18 (7.5%)
Parity	
• Nulliparous	52 (21.7%)
• Parous	188 (78.3%)

Source: Summary of Clinical Efficacy, Page 28, Table 3-10

Medical Reviewer's Comment

- *Women in the primary Study A52238 were younger as a result of the different inclusion criteria (18 to 35 years in Study A52238 vs. 21 to 40 years in Study A46796) and the proportion of nulliparous women was noticeably higher in this study.*

6.1.3 Subject Disposition

In Study A52238, a total of 3661 women were screened for inclusion in the study, leading to a total of 2885 women who were randomized. One subject was randomized but no insertion was attempted and so she was excluded from the FAS of 2884 subjects. Of the 776 women (21.2%) who were screened but not randomized, 401 did not meet the inclusion and exclusion criteria, 164 withdrew

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consent, 85 had no further information available, 44 could not be included due to pregnancy, and 82 discontinued for other reasons.

Medical Reviewer's Comment

- *LNG IUS insertion was not attempted in 1 subject (Subject 245532) in the LCS16 group due to an inability to define uterine depth on an ultrasound examination.*

During the first year of treatment, 511 subjects (17.7%) prematurely discontinued the study treatment and in the second year of treatment 397 subjects (16.7%) prematurely discontinued treatment. During the third year of treatment, the number of subjects who discontinued was fewer (285 subjects, 14.4%) but still fairly evenly distributed between the treatment groups.

Table 8 Subject Dispositions, Study A52238

Randomized (N = 2885)		
Parameter	LCS12 (N=1432)	LCS16 (N=1453)
First Year		
Insertion attempted	N=1432 (FAS)	N=1452 (FAS) ¹
Premature discontinuations	266	245
• Failed insertions	6	7
• Adverse event	175	168
• Lost to follow-up	25	21
• Withdrawal of consent	11	9
• Protocol deviation	3	0
• Pregnancy	5	2
• Other	47	46
Second year		
Started the second treatment year	N=1166	N=1206
Premature discontinuations	203	194
• Adverse event	85	66
• Lost to follow-up	23	21
• Withdrawal of consent	9	14
• Protocol deviation	5	8
• Pregnancy	3	3
• Other	78	82
Third Year		
Started the third treatment year	N=963	N=1012
Premature discontinuations	144	142
• Adverse event	53	44
• Lost to follow-up	15	19
• Withdrawal of consent	6	8
• Protocol deviation	8	8
• Pregnancy	1	5
• Other	61	57
Study Completion		
Premature discontinuations	612 (42.7%)	582 (40.0%)
Completed study	819 (57.2%)	870 (59.9%)
Pregnancies	9	10

¹ Insertion not attempted in one subject due to undefined uterine depth on ultrasound. Therefore, this subject was not included in the FAS.

Source: Adapted from CSR A52238, Page 70, Figure 8.1

Medical Reviewer's Comments

- *The majority of premature discontinuations in both treatment groups was due to an adverse event, with a slightly higher proportion occurring in the LCS12 group.*
- *The reason "other" included women who discontinued due to a wish for pregnancy (LCS12: 115, LCS16: 117), in addition to women who had no further need for contraception, who could not attend visits, or who had other personal reasons.*

Comparison was done of parous and nulliparous women who withdrew consent or who had an AE or withdrew due to any reasons that were associated directly with LNG or the IUS system such as bleeding problems, amenorrhea, and progestin-related side effects.

Table 9 Discontinuations by Parity, Study A52238

Parity	Reason for Discontinuation	LCS12 N=1432	LCS16 N=1452	Total N=2884
Nulliparous Subjects		556 (100%)	574 (100.0%)	1130 (100.0%)
	Withdrawal of consent or AE	155 (27.9%)	130 (22.6%)	285 (25.2%)
	Progestin-related side effect	21 (3.8%)	20 (3.5%)	41 (3.6%)
	Bleeding, incl. amenorrhea	29 (5.2%)	32 (5.6%)	61 (5.4%)
Parous Subjects		876 (100.0%)	878 (100.0%)	1754 (100.0%)
	Withdrawal of consent or AE	184 (21.0%)	179 (20.4%)	363 (20.7%)
	Progestin-related side effect	27 (3.1%)	20 (2.3%)	47 (2.7%)
	Bleeding, incl. amenorrhea	39 (4.5%)	39 (4.4%)	78 (4.4%)
Total Subjects		1432 (100.0%)	1452 (100.0%)	2884 (100.0%)
	Withdrawal of consent or AE	339 (23.7%)	309 (21.3%)	648 (22.5%)
	Progestin-related side effect	48 (3.4%)	40 (2.8%)	88 (3.1%)
	Bleeding, incl. amenorrhea	68 (4.7%)	71 (4.9%)	139 (4.8%)

Source: CSR A52238, Page 248, Table 14.1.1

Medical Reviewer's Comment

- *The classification of events as bleeding problems or progestin-related side effects was made by the investigator.*

In Study A52238, total drug exposure is shown below.

Table 10 Total Drug Exposure, Days and Women-Years, FAS, Study A52238

	LCS12 (N=1432)	LCS16 (N=1452)
Total duration of treatment (days)	1,174,915.0	1,223,998.0
Year 1 cumulative treatment (WY*)	1264.79	1300.02
2 years cumulative treatment (WY)	2312.04	2394.71
3 years cumulative treatment (WY)	3185.39	3315.12
Total duration of treatment (WY)	3218.95	3353.42

* A woman-year = 365 days

Source: Integrated Statistical Analysis, Page 535, Table 71

Table 11 Total Drug Exposure, 28-Day Cycle Equivalents¹, FAS, Study A52238

	LCS12 (N=1398)	LCS16 (N=1414)
Year 1 exposure in 28-day cycles	15,763	16,199
3 years cumulative exposure in 28-day cycles	39,368	41,332

Source: Integrated Statistical Analysis, Page 860, Table 98

¹ 13 28-day cycle equivalents = 1 WY

6.1.4 Analysis of Primary Endpoint(s)

6.1.4.1 Study A52238

The primary pregnancy rate was based on data from women 18 to 35 years of age during the first year of use (Year 1 PI) and for the total treatment duration of 3 years (3-year PI). The primary efficacy population included all women in the FAS, which was defined as all randomized women in whom an insertion was at least attempted. Those few women who received a LCS other than the one to which they had been randomized were analyzed “as treated” (i.e., they were assigned to the treatment arm they actually received rather than the one they had been randomized to).

Contraceptive efficacy was assessed by calculating the PI and performing a Kaplan-Meier life-table analysis based on the number of pregnancies occurring during study treatment or for which the estimated date of conception was within 7 days after the LCS12 removal or detection of expulsion. Months in which conception did not occur but which included the use of back-up contraception or exclusionary concomitant sex steroids were not included in the calculation of the PI.

Of the 2884 women who received an IUS, 1432 women were in the LCS12 group. The mean treatment duration for LCS12-treated women was 813 days or 2.23 WY.

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Medical Reviewer's Comment

- *As listed in Table 8, approximately 43% of the subjects randomized to LCS12 did not complete the full 3-year course of the study.*

A total of 20 pregnancies occurred in this study. Ten pregnancies occurred in the LCS12 treatment group. Of these, 3 (30%) were ectopic. Of the remaining 7 pregnancies in this group, 3 pregnancies ended in spontaneous abortion and 1 in induced abortion, 2 pregnancies were normal and carried to term, and 1 pregnancy was delivered prematurely by cesarean section due to preeclampsia, with a normal fetal outcome.

Ten pregnancies occurred in the LCS16 treatment group. Of these 10, 7 (70%) were ectopic. Of the 3 remaining pregnancies in the LCS16 group, 1 was a blighted ovum that ended in spontaneous abortion, 1 was a spontaneous abortion, and 1 pregnancy was normal and carried to term.

In Study A52238, there were no pregnancies documented with an estimated date of conception before the start of the study treatment or within the 7-day window post IUS removal or expulsion.

All women were contacted by the study sites after end of study to determine if they had become pregnant within 3 months after the end of the study treatment or discontinuation. One woman in the LCS12 cohort (PID 244119) became pregnant during this time period.

Medical Reviewer's Comments

- *Subject 244119 was a 24 year old woman who had her LCS12 inserted on March 27, 2008. A vaginal ultrasound exam on that date showed that the IUS was intrauterine. The subject prematurely discontinued from the trial on November 14, 2008 due to post coital bleeding. Prior to the IUS removal an ultrasound documented correct intrauterine location and the IUS was removed on November 14, 2008. At that time, her serum HCG was negative. The subject was contacted by telephone on March 10, 2009 as a routine, 3-month post-study call to ascertain whether or not a pregnancy had occurred. During that call, the subject reported that she had taken a home pregnancy test and that it was positive, but she did not provide (or the site did not record) the date of the home pregnancy test. No information was obtained at that time regarding the date of the last menstrual period, estimated conception date, or estimated date of confinement. Several subsequent attempts to contact the subject by telephone were unsuccessful. A certified letter was sent to the subject on February 10, 2010. The certified letter was returned to the site on March 28 2010 (notation: unable to forward), and no further information has since been obtained.*
- *A review of the CRF does not document any post study contact with the subject*

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and no evidence that the subject was ever pregnant. Because of the lack of information regarding dating of this pregnancy, the Applicant did not include this subject in the primary efficacy analysis. I agree that the available evidence does not warrant the inclusion of this subject as an LCS12 failure.

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Table 11 Reported Pregnancies in the LCS12 Cohort, Study A52238

Patient ID No.	Age BMI Parity Ethnicity	IUS Insertion- Removal/ Expulsion	Estimated Conception Date	Days Post Insertion	Comment
120329	23 yrs 22.5 kg/m ² Parous Hispanic	4/18/08- 9/5/10	8/7/10	841	-Total expulsion on 9/5/10. -Uterine implantation -Healthy baby
120419	30 yrs 21.8 kg/m ² Parous Caucasian	5/14/08- 2/24/09	1/4/09	235	-Ectopic pregnancy -Salpingectomy
140202	27 yrs 29 kg/m ² Nulliparous Caucasian	2/20/08- 9/3/10	8/1/10	893	-Spontaneous abortion
141008	26 yrs 21.9 kg/m ² Parous Caucasian	2/27/08- 4/29/08	4/7/08	40	-Pregnancy diagnosed 4/29 -IUS expulsion into cervix diagnosed by TVU on 4/29 -Induced first trimester abortion
160743	18 yrs 19.8 kg/m ² Nulliparous Caucasian	1/18/08- 4/27/08	4/1/08	74	-Ectopic pregnancy - Had a bicornuate uterus not detected at screening
190636	23 yrs 26.2 kg/m ² Parous Hispanic	5/19/08- 9/24/09	6/23/09	400	-Spontaneous abortion
210519	34 yrs 23.4 kg/m ² Parous Caucasian	3/12/08- 12/14/09	10/29/09	596	-Partial expulsion 12/14/09 -Preterm cesarean -Healthy baby
230303	20 yrs 22.5 kg/m ² Nulliparous Caucasian	1/14/08- 6/16/09	5/1/09	473	-Ectopic pregnancy -Laparoscopy
245003	27 yrs 21 kg/m ² Parous Caucasian	1/7/08- 11/12/08	10/3/09	270	-Spontaneous abortion
245932	27 yrs 36.7 kg/m ² Nulliparous Caucasian	5/5/08- 2/23/09	1/1/09	241	--IUS expulsion into cervix diagnosed by TVU on 2/23 -Cesarean -Healthy baby

Sources: Adapted from Summary of Clinical Efficacy, Page 56, Table 3-25 and Integrated Statistical Analysis of Safety and Efficacy, Page 856, Table 97

Medical Reviewer’s Comments

- *The earliest estimated date of conception was 40 days after insertion (Subject 141008).*
- *For Subject 160743, the TVU performed on January 18, 2008 just after the LCS insertion showed a correct intrauterine location. A bicornuate uterus was not visualized on this baseline sonogram. On April 23, 2008, an ectopic pregnancy was diagnosed. A TVU was again performed on April 27, 2008 just before the IUS was removed. The TVU confirmed the intrauterine location of the IUS however with the remark that the IUS was in the right corner of the uterus and that the left corner was empty. The diagnosis of a nonviable “extrauterine pregnancy” was made. The subject spontaneously aborted this pregnancy.*

During the first year of treatment with LCS12, a total of 5 pregnancies occurred. During the second year, 3 pregnancies occurred and during the third year of treatment, 2 pregnancies occurred.

Table 12 Reported Pregnancies During Treatment, FAS, Study A52238

	LCS12 N=1672 (100%)			
Study A52238 ¹	Implantation Site			
	Uterine	Ectopic	Other ²	Total
Year 1	3	2	0	5
Year 2	2	1	0	3
Year 3	1	0	1	2
Total	6	3	1	10

¹This study did not have any pregnancies with an estimated date of conception within 7 days after the IUS removal.

²Spontaneous abortions where no intrauterine gestation was documented
 Source: Adapted from Summary of Clinical Efficacy, Page 50, Table 3-21

Medical Reviewer’s Comment

- *The 12-month follow-up period to gather information on the return to fertility in this study is ongoing at the time of the submission. Information on return to fertility in Study A46796 is discussed in Section 7.3.5.*

Table 13 lists the calculated unadjusted PIs by year and treatment. Exposure data is based on the number of days of individual exposure converted to woman-years.

Table 13 Unadjusted PIs by Year and Treatment, Study A52238

Treatment	N	Time	Total Exposure (WY)	Relevant Exposure (WY) ¹	Pregnant	Pearl Index (95% CI)
LCS12	1432	Year 1	1280.22	1217.78	5	0.41 (0.13, 0.96)
LCS16	1452		1316.37	1252.78	2	0.16 (0.02, 0.58)
LCS12	1162	Year 2	1056.98	1015.67	3	0.30 (0.06, 0.86)
LCS16	1206		1105.32	1067.49	4	0.37 (0.10, 0.96)
LCS12	960	Year 3	870.42	825.17	2	0.24 (0.03, 0.88)
LCS16	1010		918.30	891.09	4	0.45 (0.12, 1.15)
LCS12	1432	Cumulative 2 Years	2337.20	2233.45	8	0.36 (0.15, 0.71)
LCS16	1452		2421.69	2320.27	6	0.26 (0.09, 0.56)
LCS12	1432	Cumulative 3 Years	3207.62	3058.62	10	0.33 (0.16, 0.60)
LCS16	1452		3339.99	3211.36	10	0.31 (0.15, 0.57)

¹One woman-year = 365 days. Total exposure minus the time (in months) in which backup contraception was used or sex hormones were taken for other reasons.

Source: CSR A52238, Page 84, Table 9.1

Medical Reviewer's Comments

- *Equal numbers of pregnancies occurred in the LCS12 and LCS16 groups.*
- *Overall and yearly exposure was slightly higher in the LCS16 group. However, more pregnancies occurred in the LCS12 group in Year 1.*
- *There were more pregnancies in the LCS16 group in Years 2 and 3.*
- *As discussed in Section 3.3.1, if cycles from Sites 2415 and 2434 are excluded from the efficacy calculations, the resultant Year 1 PI is 0.42 with the 95% upper limit of 0.98 for the first 13 cycles. The 3-year cumulative pregnancy rate by Kaplan-Meier method is 0.90 with the 95% upper limit of 1.68 per 100 women (the estimate including these sites is 0.9 with an upper limit of 1.7). These numbers do not affect our efficacy conclusions.*

Table 14 lists the adjusted PIs for the years of use. For the adjusted PIs, only the exposure time until the IUD was last known to be in situ or displaced in the uterine cavity, was used.

Table 14 Adjusted PIs by Year, LCS12, Study A55238

Treatment LCS12	Subjects	Total Exposure (WY)	Relevant Exposure (WY) ¹	Pregnant	Pearl Index (95% CI)
Overall	1432	3191.55	3040.95	10	0.33 (0.16, 0.60)
Year 1	1432	1270.42	1208.82	5	0.41 (0.13, 0.97)
Year 2	1155	1048.64	1008.56	3	0.30 (0.06, 0.87)
Year 3	953	863.44	818.68	2	0.24 (0.03, 0.88)
Cumulative 3 Years	1432	3182.50	3036.07	10	0.33 (0.16, 0.61)

¹Total exposure minus the time in which backup contraception was used or sex hormones were taken for other reasons

Source: Integrated Statistical Analysis of Safety and Efficacy, Page 605, Table 79

Medical Reviewer's Comment

- *The unadjusted and adjusted PIs were almost identical, since no pregnancies were excluded for the calculation of the adjusted PIs. There were only a few partial expulsions so the exposure times were almost the same as well.*

At the Pre-NDA Meeting held on July 28, 2011, the Division requested that the PI also be calculated based on completed 28-day cycle equivalents as a sensitivity analysis. The unadjusted PIs for Year 1, Year 2, Year 3 and for the 3 years of treatment for women between 18 and 35 years of age using the 28-day cycle exposure data (i.e., 1 WY equals 13 cycles; time with back-up contraception subtracted in terms of 28-day cycles) are shown below.

Table 15 PI Based on 28-Day Cycle Equivalents, LCS12, Study A52238

Time	Subjects	Relevant Exposure (WY)	Relevant Exposure (Cycle)	No. Preg.	PI CI
Year 1	1398	1212.54	15763	5	0.41 (0.13, 0.96)
Year 2	1135	1014.08	13183	3	0.30 (0.06, 0.86)
Year 3	938	801.69	10422	2	0.25 (0.03, 0.90)
Cum. 3 Years	1398	3028.31	39368	10	0.33 (0.16, 0.61)

Source: Integrated Statistical Analysis of Safety and Efficacy, Page 860, Table 98

Medical Reviewer's Comments

- *The PI analysis based on 28-day cycles did not reveal any significant differences compared to the PI analysis based on the exposure in woman-years.*
- *EMA requirements for efficacy for a long acting reversible contraceptive (such as LCS12) is that the difference between the point estimate for the PI and the upper bound of the CI should not exceed 1. This requirement for efficacy is clearly met at the Year 1 and cumulative 3 Year primary efficacy endpoints.*

The unadjusted Pearl Indices stratified by age, parity and BMI are shown below.

Table 16 Unadjusted PIs, LCS12, Subgroups, Study A55238

	LCS12		
	Women/ Pregnancies	Relevant Exposure in Women/Years ¹ (WY)	PI, Upper 95% CI
PI by Age Year 1			
18-35 years	1432 / 5	1217.78	0.41, 0.96
18-25 years	566 / 1	455.62	0.22, 1.22
26-35 years	866 / 4	762.15	0.52, 1.34
PI by Age Cumulative 3-year			
18-35 years	1432 / 10	3058.62	0.33, 0.60
18-25 years	566 / 4	1114.21	0.36, 0.92
26-35 years	866 / 6	1944.41	0.31, 0.67
PI by Parity Year 1			
Nulliparous	556 / 2	446.88	0.45, 1.62
Parous	876 / 3	770.90	0.39, 1.14
PI by Parity Cumulative 3-Year			
Nulliparous	556 / 4	1110.63	0.36, 0.92
Parous	876 / 6	1947.99	0.31, 0.67
PI by BMI Year 1			
< 30kg/m ²	1187 / 9	1009.73	0.40, 1.01
≥ 30kg/m ²	244 / 1	207.13	0.48, 2.69
PI by BMI Cumulative 3-Year			
< 30kg/m ²	1187 / 9	2547.32	0.35, 0.67
≥ 30kg/m ²	244 / 1	509.34	0.20, 1.09

¹ 1 WY = 365 days

Source: Summary of Clinical Efficacy, Page 63, Table 3-26

Medical Reviewer's Comment

- *There were no relevant differences in the PIs of any subgroup.*

Table 17 Unadjusted Cumulative Failure Rates (Kaplan-Meier Analysis), LCS12, Subgroups, Study A55238

	LCS12		
	Women/ Pregnancies	Relevant Exposure in Women/Years (WY)	Cumulative Failure Rate, (95% CI)
Cumulative failure rates by year for women 18-35 years			
Year 1	1432 / 5	1217.78	0.004 (0.002, 0.010)
Year 2	1162 / 3	1015.67	0.003 (0.001, 0.009)
Year 3	960 / 2	825.17	0.002 (0.001, 0.009)
Cum. 3-year	1432 / 10	3058.62	0.009 (0.005, 0.017)
Cumulative, 3-year failure rate for women 18 to 35 years by age			
18-35 years	1432 / 10	3058.62	0.009 (0.005, 0.017)
18-25 years	566 / 4	1114.21	0.010 (0.004, 0.027)
26-35 years	866 / 6	1944.41	0.008 (0.004, 0.019)
Cumulative, 3-year failure rate for women by parity			
Nulliparous	556 / 4	1110.63	0.010 (0.004 0.026)
Parous	876 / 6	1947.99	0.009 (0.004 0.019)
Cumulative, 3-year failure rate for women by BMI			
< 30kg/m ²	1187 / 9	2547.32	0.010 (0.005, 0.019)
≥ 30kg/m ²	244 / 1	509.34	0.005 (0.001, 0.033)

Source: Summary of Clinical Efficacy, Page 70, Table 3-29

Medical Reviewer's Comments

- *Per the FDA Statistician's calculations, based on 28-day cycle equivalents, the cumulative pregnancy rate at the end of the first year is 0.0039 (0.0016 to 0.0094) and at the end of the third year is 0.0089 (CI is 0.0048 to 0.0166).*
- *The probability of getting pregnant using LCS12 over 3 years in various subgroups is shown above. Similar to the PIs, there were no relevant differences in terms of age, parity or BMI.*
- *The PI and Kaplan-Meier calculations based on data derived from primary Study A55238 strongly support the efficacy of LCS12 over the 3 year time period.*

6.1.4.2 Study A46796

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

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Of the 742 women:

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

The mean treatment duration was:

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

Medical Reviewer's Comments

- *Evidence for the approval of LCS12 was based only on the pivotal phase 3 study. The phase 2 study was submitted as supportive. This study was primarily a dose-finding study and was not adequately powered to determine precise PIs for each dose.*
- *The comparators used in this phase 2 study were LCS16 and Mirena. There were no pregnancies in the Mirena arm, which consisted of only 254 subjects. This review will concentrate mainly on the LCS12 arm of the study.*
- *Inclusion criteria for this study included women ages 21 to 40. The PI is usually derived from the 18-35 age group, so only this cohort will be reviewed for efficacy.*

A total of 7 pregnancies occurred in this study. Two of these pregnancies were observed in the LCS12 group; an ectopic pregnancy occurred in the second year of treatment and an intrauterine pregnancy occurred approximately 2 days post IUS removal. Both pregnancies occurred in the 18-35 age group.

A total of 5 pregnancies occurred in the LCS16 group. Two of these 5 pregnancies were ectopic (40%) and 2 ended in a spontaneous abortion. The remaining pregnancy in this group occurred in a patient who had an unnoticed expulsion of the IUS. This pregnancy was normal and carried to term.

There were no pregnancies in the Mirena group.

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Table 18 Reported Pregnancies, LCS12 Cohort, Study A46796

Patient ID No.	Age BMI Parity Ethnicity	IUS Insertion- Removal	EDC*	Days Post Insertion	Comment
20568	33 yrs 30 kg/m ² Parous Caucasian	9/4/05 - 4/3/06	4/5/06	213	-Discontinued because of a wish for pregnancy -Estimated date of conception 2 days after IUS removal. -Delivered (b) (6)
130221	27 yrs 24.3 kg/m ² Parous Caucasian	7/6/05 - 1/28/07	1/19/07	562	-Ectopic pregnancy

*Estimated date of conception

Source: Adapted from Summary of Clinical Efficacy, Page 58, Table 3-25

Medical Reviewer's Comment

- *Although Subject 20568's conception date is after the IUS was removed, it is still considered an IUS failure and relevant to the PI calculation, because the Division's convention is to include a margin of 7 days after discontinuation of birth control to account for variability in pregnancy dating. This was the only LCS12 pregnancy in both studies to have occurred in the 7 days post IUS removal.*

The Year 1 PI for the LCS12 group in women 18-35 years of age in this study, based on a relevant exposure of 144.51 WY, was 0.69 (0.02, 3.86). The cumulative 3-year PI for the LCS12 group, based on a relevant exposure of 369.88 WY, was calculated as 0.54 (0.07, 1.95).

Table 19 Unadjusted PIs, 18-35 years, LCS12, Study A46796

	LCS12			
	No. of Women/No. of Pregnancies	Relevant Exposure* (WY)	Pearl Index	Upper 95% CI
Year 1	154/1	144.51	0.69	(0.02, 3.86)
Year 2	138/1	121.38	0.82	(0.02, 4.59)
Year 3	115/0	103.99	0.00	(0.00, 3.55)
Cum. 3-Year	154/2	369.88	0.54	(0.07, 1.95)

*Total exposure time excluding the time in which concomitant contraception was used or sex steroids were taken for any reason.

Sources: Adapted from the Summary of Clinical Efficacy, Page 65 of 93, Table 3-27 and Integrated Statistical Analysis of Safety and Efficacy, Page 684, Table 84

Medical Reviewer's Comment

- *The number of women randomized to LCS12 was relatively small (n=240) in this study, hence the wide CIs.*

6.1.4.3 Pooled Studies

For the pooled analysis of subjects ages 18-35 across both studies, a total of 1586 women were assigned to the FAS of LCS12. The relevant exposure was 3434.90 WY. A total of 12 pregnancies occurred.

Table 20 Full Analysis Set, LCS12, Women 18-35 years, Pooled Data

	LCS12
Study A52238	1432
Study A46796*	154
Pooled data	1586

* Excluded 1 woman with an unsuccessful insertion
 Source: Summary of Clinical Efficacy, Page 17 of 93, Table 3-1

Medical Reviewer's Comment

- *In Study A46796, the age inclusion criterion was 21-40. Of the 240 women randomized to LCS12, 154 were between the ages of 18 to 35 and included in the efficacy analysis.*

Table 21 Unadjusted PIs, Women 18-35 years, LCS12, Pooled Data

	LCS12			
	No. of Women/No. of Pregnancies	Relevant Exposure* (WY)	Pearl Index	Upper 95% CI
Year 1	1586 /6	1362.29	0.44	(0.16, 0.96)
Year 2	1300 / 4	1137.05	0.35	(0.10, 0.90)
Year 3	1075 /2	929.16	0.22	(0.03, 0.78)
Cum. 3-Year	1586/12	3428.50	0.35	(0.18, 0.61)

*Total exposure time excluding the time in which concomitant contraception was used or sex steroids were taken for any reason.

Sources: Integrated Statistical Analysis of Safety and Efficacy, Page 688, Table 84

Medical Reviewer's Comments

- *Overall, a total of 12 pregnancies occurred over 3434.90 WY in women randomized to LCS12. 50% of these occurred in year 1.*
- *The pooled study data shown above support the efficacy of LCS12 for intrauterine contraception for up to 3 years.*

Table 22 below summarizes the unadjusted 3-year PIs for subgroups by age, parity and BMI.

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Table 22 Unadjusted PIs, LCS12, Subgroups, All Women, Pooled Data

	LCS12		
	Women/ Pregnancies	Relevant Exposure in Women/Years (WY)	PI, Upper 95% CI
PIs By Treatment Year(s), Women 18-35 Years			
Year 1 PI	1586 / 6	1362.29	0.44 , 0.96
Year 2 PI	1399 / 4	1137.05	0.35 , 0.90
Year 3 PI	1075 / 2	929.16	0.22 , 0.78
Cum. 3-year PI	1586 / 12	3428.50	0.35 , 0.61
Year 1 PI by Age			
18-35 years	1586 / 6	1362.29	0.44 , 0.96
18-25 years	604 / 1	490.70	0.20 , 1.14
26-35 years	982 / 5	871.59	0.57 , 1.34
> 35 years	86 / 0	80.62	0.00 , 4.58
Year 1 PI by Parity			
Nulliparous	608 / 2	492.16	0.41 , 1.47
Parous	1064 / 4	950.75	0.42 , 1.08
Year 1 PI by BMI			
< 30kg/m ²	1409 / 4	1219.39	0.33 , 0.84
≥ 30kg/m ²	262 / 2	222.60	0.90 , 3.25
3-year PI by Age			
18-35 years	1586 / 12	3428.50	0.35 , 0.61
18-25 years	604 / 4	1193.86	0.34 , 0.86
26-35 years	982 / 8	2234.64	0.36 , 0.71
> 35	86 / 0	225.19	0.00 , 1.64
3-Year PI by Parity			
Nulliparous	608 / 4	1218.48	0.33 , 0.84
Parous	1064 / 8	2435.21	0.33 , 0.65
3-Year PI by BMI			
< 30kg/m ²	1409 / 10	3099.89	0.32 , 0.59
≥ 30kg/m ²	262 / 2	551.84	0.36 , 1.31

Source: Adapted from Summary of Clinical Efficacy, Page 68, Table 3-28

Medical Reviewer's Comments

- *There are no relevant differences in the PIs between the primary Study A52238 and the pooled analysis, which is not unexpected because the pooled data is mostly driven by Study A52238, which had most of the pregnancies (10 vs. 2).*

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- *Unadjusted Year 1 and 3-year PIs were similar for parous and nulliparous women.*
- *The subgroup of women with a BMI $\geq 30\text{kg/m}^2$ resulted in a PI of 0.90 at 1 year however the upper bound of 3.25 reflected the small size of this cohort.*

The unadjusted cumulative failure rate over 3 years of treatment is shown below.

Table 23 Cumulative Failure Rates (Kaplan-Meier Analysis) by Year and Subgroup, LCS12, Pooled Data

	LCS12		
	Women/ Pregnancies	Relevant Exposure in Women/Years (WY)	Cumulative Failure Rate, (95% CI)
Cumulative failure rate by year for women 18-41 years			
Year 1 PI	1672 / 6	1442.91	0.004 (0.002, 0.009)
Year 2 PI	1377 / 4	1211.45	0.003 (0.001, 0.009)
Year 3 PI	1147 / 2	999.34	0.002 (0.000, 0.008)
Cumulative, 3-year failure rate for women 18-41 years			
18-35 years	1586 / 12	3428.50	0.010 (0.005, 0.017)
18-25 years	604 / 4	1193.86	0.009 (0.003, 0.025)
26-35 years	982 / 8	2234.64	0.010 (0.005, 0.020)
> 35	86 / 0	225.19	0.000 (0.000, 0.000)
All women	1672 / 12	3653.69	0.009 (0.005, 0.016)
Cumulative, 3-year failure rate for women by parity			
Nulliparous	608 / 4	1218.48	0.009 (0.003, 0.024)
Parous	1064 / 8	2435.21	0.009 (0.005, 0.018)
Cumulative, 3-year failure rate for women by BMI			
< 30kg/m ²	1409 / 10	3099.89	0.009 (0.005, 0.017)
$\geq 30\text{kg/m}^2$	262 / 2	548.13	0.009 (0.002, 0.035)

Source: Summary of Clinical Efficacy, Page 74, Table 3-31

Medical Reviewer's Comment

- *Subgroup analysis did not show significant differences in terms of the probability of pregnancy after 3 years.*

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6.1.5 Analysis of Secondary Endpoints

6.1.5.1 Bleeding

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

Medical Reviewer's Comments

- *The Applicant used data based on 90-day reference periods over the entire course of treatment as recommended by the WHO. However, at the pre-NDA Meeting of July 28, 2011, the Division requested that bleeding data also be analyzed in terms of completed 28-day reference periods, as this would be more relevant to clinicians.*
- *Results from the Mirena group from Study A46796 will not be discussed because the sample size is too small compared to the sample sizes in the LCS12 and LCS16 treatments.*

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Table 24 Subjects with at Least One Bleeding/Spotting Day, LCS12, Pooled Data

28-Day Reference Period N	# (%) with at least one bleeding or spotting day	Number of Bleeding/Spotting Days Mean (SD) /Median
1 1588	1579 (99.4%)	16.5 (7.5)/17.0
2 1576	1515 (96.1%)	12.3 (7.2)/11.0
3 1558	1448 (92.9%)	9.9 (6.7)/9.0
4 1535	1399 (91.1%)	8.3 (5.8)/8.0
5 1517	1341 (88.4%)	7.3 (5.4)/7.0
6 1501	1300 (86.6%)	6.9 (5.2)/6.0
9 1429	1200 (84.0%)	5.8 (4.6)/5.0
12 1361	1125 (82.7%)	5.4 (4.4)/5.0
24 1156	917 (79.3%)	4.6 (4.1)/4.0
36 991	764 (77.1%)	4.2 (3.6)/4.0

Source: Integrated Statistical Analysis, Tables 171 and 175

Medical Reviewer's Comment

- *The mean number of bleeding days decreased over time.*

Table 25 Subjects by 90-Day Reference Periods, Bleeding, LCS12, Pooled Data

90-Day Reference Period/ #Subjects	Amenorrhea ¹	Infrequent Bleeding ²	Frequent Bleeding ³	Irregular Bleeding ⁴	Prolonged Bleeding ⁵	Normal Bleeding ⁶
1/ 1531 (100%)	5 (0.3%)	129 (8%)	468 (31%)	643 (42%)	903 (59%)	230 (15%)
2/ 1475 (100%)	44 (3%)	282 (19%)	180 (12%)	415 (28%)	249 (17%)	532 (36%)
3/ 1399 (100%)	80 (6%)	286 (20%)	114 (8%)	329 (24%)	146 (10%)	573 (41%)
4/ 1329 (100%)	83 (6%)	271 (20%)	100 (7.5%)	300 (23%)	118 (9%)	562 (42%)
12/ 903 (100%)	105 (12%)	201 (22%)	36 (4%)	416 (46%)	27 (3%)	144 (16%)

¹ Amenorrhea is defined as no bleeding or spotting during a reference period

² Infrequent bleeding is defined as 1 or 2 bleeding/spotting episodes during a reference period

³ Frequent bleeding is defined as more than 5 bleeding/spotting episodes during a reference period

⁴ Irregular bleeding is defined as 3 to 5 bleeding/spotting episodes and less than 3 bleeding/spotting-free intervals of 14 or more days

⁵ Prolonged bleeding is defined as bleeding/spotting episodes lasting longer than 14 days during a reference period.

⁶ Normal bleeding is defined as no amenorrhea, infrequent bleeding, frequent bleeding, irregular bleeding or prolonged bleeding.

Source: Integrated Statistical Analysis, Table 137

Medical Reviewer's Comments

- *Amenorrhea develops gradually with continued use.*
- *Prolonged bleeding decreases substantially with continued use.*

6.1.6 Other Endpoints

A pharmacokinetics analysis set (PKS) was defined for the women in subset 3 in each clinical trial with valid data for PK analysis.

Medical Reviewer's Comment

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

6.1.7 Subpopulations

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

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6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The Applicant is currently seeking approval of only one dose of LNG for the IUS. Study A52238 is ongoing to provide 5-year data on the efficacy of the LCS16.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

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

6.1.10 Additional Efficacy Issues/Analyses

No additional efficacy issues/analyses were presented.

7 Review of Safety

Safety Summary

The bulk of the LCS12 safety database consists of the primary phase 3 study, A52238 (performed in Europe, North America and South America) and the comparative phase 2 study A46796 (performed in Europe). All women who were enrolled and had an insertion attempt were included in the safety analysis. A total of 1672 women, including 1,383 exposed for one year and 993 who completed the 3-year study, were assigned to the LCS12 cohort. The population was generally healthy, 18 to 40-year old females requesting contraception and predominately Caucasian (82.6%). Safety was analyzed based on data pooled across the two studies.

The safety profile of LCS12 did not raise any specific safety concerns.

The most common adverse reactions reported in the clinical trials included bleeding pattern alterations, vulvovaginitis, abdominal/pelvic pain and acne/seborrhea. Other drug-related AEs were similar to those that are known to occur with the use of Mirena and included ovarian cyst, and dysmenorrhea). The relative frequency of SAEs was low. The most common AEs causing discontinuation of study drug were vaginal hemorrhage, device expulsion, and acne. The frequencies of the IUS-related and other significant AEs did not raise any safety concerns either. A total of 4 ectopic pregnancies occurred during treatment with LCS12, resulting in an overall incidence of 0.11 per 100 WY (pooled data). There were no significant safety problems found in the nulliparous subjects. There were no safety relevant effects observed with regard to laboratory tests, vital signs, bone mineral density and other safety parameters measured.

In summary, LCS12 was demonstrated to be safe in women 18-41 years of age for the proposed 3 year duration of use.

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7.1 Methods

Subjects with both successful and unsuccessful insertions were included in the safety evaluation for Study A52238. The assignment of the women to the FAS in Study A46796 only included women with a successful IUS insertion. For the pooled analysis, the FAS included data from all randomized women who had an IUS insertion attempt. This definition differed from that used in Study A46796 so three women in A46796 were used in the pooled FAS but were not part of the Study A46796 FAS population. Only one of these three women was in the LCS12 group.

Medical Reviewer's Comment

- *The difference between the FAS in the study report for Study A46796 and the pooled data is very small and has no impact on the safety assessment.*

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Evidence for the clinical safety of LCS12 is based on the phase 3 study (A52238, performed in Europe, North and South America) between 2007 and 2011 and the phase 2 clinical study (A46796, performed in Europe) conducted between 2005 and 2011. The safety data from these studies are presented mainly as a pooled analysis.

There were some differences between these two studies in population and size.

- The women in Study A52238 (inclusion age 18 to 35 years) were slightly younger than those in Study A46796 (inclusion age 21 to 40 years). The actual age range of subjects was 18-35 in Study A52238 and 20 to 41 in Study A46796.
- Subjects in A52238 came from a broader geographic population (Europe, US, Canada, South America) than those in Study A46796 (Europe only).
- Study A52238 had a much larger population and a higher proportion of nulliparous women than Study A46796.

Safety variables evaluated were AEs, concomitant medication, laboratory tests, vital signs, general physical, breast, gynecological examinations, and pap smears. Safety variables of special interest are pelvic inflammatory disease, IUS expulsions and perforations, and ectopic pregnancies. Further safety evaluations included rate and intensity of dysmenorrhea (Study A52238 only), IUS insertion/removal ease and pain; and endometrial safety; and bone mineral density, and hemostatic safety (subgroups in Study A52238 only).

Adverse events were analyzed by age, parity, ethnicity, body mass index, and time. A stratification by age, parity, and/or time was also done for selected safety parameters including pelvic inflammatory disease, IUS expulsion, perforation, certain reasons leading to discontinuation (progestin-related side effects, bleeding problems or bleeding

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abnormalities (including amenorrhea), IUS insertion/removal ease, and insertion/removal pain, and compliance.

7.1.2 Categorization of Adverse Events

All serious adverse events and common adverse events were reported using MedDRA (version 14.0).

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

In Study A52238, 2884 women were assigned to the FAS for the assessment of safety, among them 1432 in the LCS12 group and 1452 in the LCS16 group. In Study A46796, a total of 741 women were assigned to the FAS for whom the insertion of an IUS was attempted, among them 240 in the LCS12 group, 245 in the LCS16 group and 256 in the Mirena group

Using the pooled data from Studies A52238 and A46796 resulted in 1672 women assigned to LCS12, 1697 women assigned to LCS16, and 256 women assigned to Mirena. More than 80% of the women in the pooled LCS12 group were from A52238 study. A total of 3625 women between the ages of 18 to 41 were studied for safety.

Table 26 Full Analysis Set, Safety Cohort, Women Ages 18-40

	LCS12	LCS16	Mirena
Study A52238	1432	1452	0
Study A46796*	240	245	256
Pooled data	1672	1697	256

*The Clinical Study Report excluded women with unsuccessful insertion from the FAS: 1 in the LCS12 group and 2 in the Mirena group.

Source: Summary of Clinical Safety, Page 23, Table 1-3

7.2 Adequacy of Safety Assessments

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

In Study A52238, 1432 women were in the LCS12 group and 1452 women were in the LCS16 group. The mean treatment duration for LCS12-treated women was 813 days or 2.23 women years (WY) and 835 days or 2.29 WY for LCS16-treated women.

In Study A46796, 240 women were in the LCS12 group, 245 women in the LCS16 group and 256 women in the Mirena group. The mean treatment duration was 915 days or 2.51 WY in the LCS12 group, 912 days or 2.50 WY in the LCS16 group, and 895 days or 2.45 WY in the Mirena group.

Table 27 Treatment Duration, FAS, Studies A52238 and A46796

	Study A52238		Study A46796			Pooled
	LCS 12	LCS16	LCS12	LCS16	Mirena	LCS12
Year 1 (N)	1432 insertions and insertion attempts	1452 insertions and insertion attempts	240 insertions	245 insertions	256 insertions	1672 1383 exposed for one year
Beginning of Year 2 (N)	1166	1206	215	212	218	1381 exposed for one year
Beginning of Year 3 (N)	963	1012	187	189	193	1150 exposed for two years
Completed Study	819 (57.2%)	870 (59.9%)	174 (72.5%)	174 (71.0%)	183 (71.5%)	993 (59.4%)
Mean (WY) ¹	2.25	2.31	2.51	2.50	2.45	2.29
Median (WY) ¹	2.97	2.98	2.99	2.99	2.99	2.97
Maximum (WY) ¹	3.3	3.4	3.2	3.1	3.1	3.3
Total (WY) ¹	3218.95	3353.42	601.71	611.91	627.95	3820.66

¹A woman year equals 365 days

Source: Adapted from Integrated Analysis, Table 71.

For the pooled analysis, the mean treatment duration for all women treated with LCS12 was 834 days or 2.29 WY, and 853 days or 2.34 WY for all women on LCS16.

Table 28 Treatment Duration (Woman Years), FAS, Pooled Data

	LCS12	LCS16	Mirena
N (subjects)	1672	1697	256
Women-Years			
Mean	2.29	2.34	2.45
Median	2.97	2.98	2.99
Maximum	3.3	3.4	3.1
Year 1	1487.90	1530.42	236.30
Year 2	2729.48	2821.07	435.13
Year 3	3778.55	3918.27	619.18
Total	3820.66	3965.33	627.95

Source: Adapted from Integrated Analysis, Table 7 and Table 77

Medical Reviewer's Comments

- The pooled data cover about 40,000 cycles of exposure.
- This review will focus primarily on the safety of LCS12.

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7.2.2 Explorations for Dose Response

Two doses of LNG (LCS12 and LCS16) were studied in both the phase 2 and phase 3 clinical trials. Both doses demonstrated similar efficacy and safety, but approval is currently being sought only for the lower of the two doses as a 3-year intrauterine contraceptive.

7.2.3 Special Animal and/or In Vitro Testing

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

7.2.4 Routine Clinical Testing

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

7.2.5 Metabolic, Clearance, and Interaction Workup

Not applicable for this submission.

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

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

7.3 Major Safety Results

7.3.1 Deaths

There was one death in Study A52238, a suicide in a 20 year-old woman (Subject 210112) related to problems with depression and an eating disorder. This subject was in the LCS16 cohort. Her death was assessed by the investigator as unrelated to study drug. There were no deaths in Study A46796.

Medical Reviewer's Comment

- *Subject 210112 was a 20 year old Caucasian woman who did not report any depression or similar disorders prior to enrollment. A LCS16 was inserted on January 11, 2008. She committed suicide in July of 2010. The reasons for her suicide were unknown. The woman's friends reported that she had depression and eating disturbances. Due to the subject's suicide, the LCS12 was never removed.*

The table below lists some of the more significant vascular disorder that occurred during Studies A52238 and 46796. The only venous thrombotic event that occurred in either

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trial was in Subject 140807 in the LCS12 group in Study A52238. None of these events were assessed by the investigator as being drug-related.

Table 29 Vascular Disorders, FAS, LCS12, Pooled Data

Study Subject Age Race	SOC/ Preferred term	Related to study drug	Study onset day/ Duration	Treatment / Study drug action	Outcome / Comment
A52238 140807 33 Caucasian	Vascular disorders/ Deep vein Thrombosis/Left leg	No	Day 201 / 15 days	LCS12 / Drug Withdrawn 2 years after the event occurred	recovered, resolved, positive family history and prior immobilization (airplane travel)
A52238 160329 21 Caucasian	Injury, poisoning and procedural complications/ Astrocytoma and tumor resection Subsequent shunt occlusion	No	Day 51 / 22 days	LCS12 / Dose not changed	recovered, resolved surgery for brain tumor with postop complications
A46796 140642 30 Caucasian	Surgical and medical procedures/ Phlebectomy/left leg vein stripping	No	Day 162 / 1 day	LCS12 / Dose not changed	recovered, resolved
A46796 150213 33 Caucasian	Nervous system disorders/ Suspected TIA	No	Day 695 / 1 day	LCS12 / Dose not changed	recovered, resolved

Source: Summary of Clinical Safety, Page 96, Table 2-37, Integrated Statistical Analysis of Safety, Page 3064-3065, Table 226

Medical Reviewer's Comments

- *Subject 160329 had a craniotomy for an astrocytoma, had postoperative complications (meningitis, subdural hematoma) and required a shunt. The shunt became occluded and required a reoperation.*
- *Subject 150213 was diagnosed with a suspected mild TIA. No VTE was documented. She fully recovered within 1 day without therapy and the event was considered non-serious by the investigator.*
- *Subject 140642 had an uncomplicated vein stripping of the left leg.*

7.3.2 Nonfatal Serious Adverse Events

In the pooled analysis, SAEs were reported in 78 women (4.7%) in the LCS12 treatment group. The most frequent SAE in this group was appendicitis. Ectopic pregnancy occurred in 4 (0.2%) subjects.

Table 30 Most Frequent SAEs, FAS, Pooled Data

	LCS12 N=1672 (100%) n (%)	LCS16 N=1697 (100%) n (%)	Mirena N=256 (100%) n (%)
Any SAE	78 (4.7)	83 (4.9)	16 (6.3)
Appendicitis	6 (0.4)	8 (0.5)	2 (0.8)
Abdominal pain	5 (0.3)	4 (0.2)	1 (0.4)
Unruptured/ ruptured Ectopic pregnancy*	4 (0.2)	9 (0.5)	0
Pneumonia	3 (0.2)	2 (0.1)	0
Ovarian germ cell teratoma, benign	3 (0.2)	2 (0.1)	0
Abortion spontaneous	3 (0.2)	4 (0.2)	0
Pelvic Inflammatory Disease*	2 (0.1)	5 (0.3)	1 (0.4)
Cholecystitis	2 (0.1)	2 (0.1)	1 (0.4)
Goiter	2 (0.1)	1 (<0.1)	0
Pyelonephritis	2 (0.1)	1 (<0.1)	0
Urinary tract infection	2 (0.1)	0	0
Thyroid cancer	2 (0.1)	0	0
Hemorrhagic ovarian cyst	2 (0.1)	0	0
Ovarian cyst*	1 (<0.1)	2 (0.1)	5 (2.0)
Cholelithiasis	1 (<0.1)	2 (0.1)	0
Chest pain	1 (<0.1)	1 (<0.1)	0
Cholecystitis chronic	1 (<0.1)	1 (<0.1)	0
Cellulitis	1 (<0.1)	1 (<0.1)	0
Peritonsillar abscess	1 (<0.1)	1 (<0.1)	0
Post procedural hematoma	1 (<0.1)	0	1 (0.4)
Subdural hematoma	1 (<0.1)	0	1 (0.4)
Paresthesia	1 (<0.1)	1 (<0.1)	0
Anxiety	1 (<0.1)	1 (<0.1)	0
Depression	1 (<0.1)	1 (<0.1)	0
Ovarian cyst ruptured*	1 (<0.1)	1 (<0.1)	0
Asthma	1 (<0.1)	1 (<0.1)	0
Detoxification	1 (<0.1)	1 (<0.1)	0

* Assessed by investigator as drug-related in the LCS12 group

Source: Adapted from Summary of Clinical Safety, Page 58, Table 2-10

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Of the 78 SAEs reported in the LCS12 group, 10 (0.6%) were assessed by the investigator to be related to the study drug. The most common study drug-related SAEs were ectopic pregnancy (3), ovarian cysts (2), and pelvic inflammatory disease (2). Other drug-related SAEs included 1 case of a spontaneous abortion, 1 case of an adhesolysis in a woman with a dermoid cyst, and 1 case of abdominal pain. An additional case of severe uterine cramps in a 19 year old woman was assessed by the investigator as being related to protocol required procedures but not drug related.

Of the 78 subjects in the LCS12 group who experienced an SAE, 15 (0.9%) discontinued the study. Of the 10 subjects with drug-related SAEs, 7 had the drug withdrawn and 3 continued therapy with LCS12.

Medical Reviewer's Comments

- *Only a total of 10 of the SAEs were considered by the investigator to be related to use of LCS12. Although there were 4 ectopic pregnancies reported in the LCS12 group, one occurred in a patient with a bicornuate uterus and was not considered by the investigator to be drug-related.*
- *The SAE profile was similar between the two treatment groups. It is of interest that the rate of ectopic pregnancy in the LCS16 group was more than twice that in the LCS12 group*

7.3.3 Dropouts and/or Discontinuations

The frequency of women who discontinued study drug due to an AE or SAE is shown below for the pooled data. In the LCS12 cohort, a total of 361 subjects who terminated prematurely from the study (21.6%) did so due to an AE and 15 subjects (0.9%) discontinued due to an SAE, for a total of 23% of discontinuations occurring due to an AE.

Table 31 Adverse Events Causing Discontinuation by Study Drug, Pooled Data

AE causing study drug discontinuation	LCS12 N = 1672 (100%)	LCS16 N = 1697 (100%)
Any Adverse Event	361 (21.6%)	337 (19.9%)
Vaginal hemorrhage	55 (3.3%)	50 (2.9%)
Device expulsions, total	54 (3.2%)*	51 (3.0%)*
Device expulsions reported as AEs	45 (2.7%)	39 (2.3%)
Acne	45 (2.7%)	33 (1.9%)
Pelvic pain	29 (1.7%)	39 (2.3%)
Abdominal pain	23 (1.4%)	16 (0.9%)
Dysmenorrhea	21 (1.3%)	13 (0.8%)
Abdominal pain lower	19 (1.1%)	12 (0.7%)
Weight increased	11 (0.7%)	21 (1.2%)
Uterine spasm	11 (0.7%)	8 (0.5%)
Depression	9 (0.5%)	3 (0.2%)
Dyspareunia	9 (0.5%)	9 (0.5%)
Abdominal distension	8 (0.5%)	4 (0.2%)
Headache	8 (0.5%)	8 (0.5%)
Libido decreased	8 (0.5%)	10 (0.6%)
Mood altered	8 (0.5%)	9 (0.5%)
Uterine hemorrhage	8 (0.5%)	3 (0.2%)
Metrorrhagia	7 (0.4%)	6 (0.4%)
Ovarian cyst	4 (0.2%)	7 (0.4%)
Device dislocation**	3 (0.2%)	7 (0.4%)

A woman may have had more than one AE

*Not all expulsions were reported as an AE

**Dislocation events include a partial perforation of the myometrium (an SAE; Study A52238) and 9 partial expulsions

Source: Summary of Clinical Safety, Page 69, Table 2-16

Medical Reviewer's Comment

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

7.3.4 Significant Adverse Events

7.3.4.1 Pregnancy, Puerperium and Perinatal Conditions

Within the MedDRA system organ class (SOC) of pregnancy conditions, the table below lists the most frequent complications in the LCS12, LCS16 and Mirena cohorts.

Table 32 Frequency of Pregnancy-Related Complications, Pooled Data

Condition	LCS12	LCS16	Mirena
	N = 1672 (100%) n (%)	N = 1697 (100%) n (%)	N = 256 (100%) n (%)
Any Condition	8 (0.5%)	15 (0.9%)	0
Ectopic pregnancy	4 (0.2%)	9 (0.5%)	0
Abortion spontaneous	3 (0.2%)	1 (<0.1%)	0
Premature separation of placenta	1 (<0.1%)	0	0
Uterine contractions abnormal	1 (<0.1%)	1 (<0.1%)	0
Abortion spontaneous incomplete	0	1 (<0.1%)	0
Blighted ovum Pregnancy	0	2 (0.1%)	0
Ruptured ectopic pregnancy	0	1 (<0.1%)	0

Source: Summary of Clinical Safety, Page 83, Table 2-26

The most frequently occurring condition within this SOC was ectopic pregnancy

Ectopic Pregnancies

There were a total of 12 pregnancies in the LCS12 cohort in the two trials. Of these 12 pregnancies, 4 (33% of all pregnancies) were ectopic. In the LCS16 cohort, there were a total of 15 pregnancies of which 9 (60%) were ectopic. No ectopic pregnancies occurred in the Mirena group.

Medical Reviewer's Comments

- *If a pregnancy occurs with an IUD in place, it is more likely to be an ectopic pregnancy, as documented by the percentages above. The 33% rate of ectopic pregnancy (as a percent of all pregnancies) demonstrated in the LCS12 group is not surprising for an IUD. The Mirena label states that up to half of pregnancies that occur with Mirena in place are ectopic.*
- *Historical prospective data from randomized controlled trials describe a low absolute risk of ectopic pregnancy, which is also reflected in the data for LCS12 from the two clinical trials submitted to this NDA, which demonstrate a 0.2% risk of an ectopic pregnancy over 3 years of use (see Table 34). Per the Mirena label, the incidence of ectopic pregnancy in clinical trials that excluded women with risk factors for ectopic pregnancy was approximately 0.1% per year.*

In Study A52238, there were a total of 3 ectopic pregnancies in the LCS12 group. Of these, one woman had a spontaneous tubal abortion of the ectopic pregnancy. This

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woman had a bicornuate uterus detected 3 months post IUD insertion. Another ectopic pregnancy occurred 9 months after insertion, for which a salpingectomy was done. The third ectopic occurred 17 months after insertion. She recovered after laparoscopic removal of an ovarian pregnancy.

In Study A46796, there was one ectopic pregnancy in the LCS12 group. This pregnancy occurred 19 months after insertion. The woman recovered following salpingectomy.

Information on these ectopic pregnancies is shown in Table 33.

Table 33 Ectopic Pregnancies with LCS12, Pooled Data

Study/Subject/ Age/Race/Parity	Study Onset Day	AE duration (days)	Study drug action	Outcome
<u>A52238 /120419/</u> 30/Caucasian/ Parous	Day 259	7 days	Drug withdrawn	Recovered, Resolved
<u>A52238 /160743/</u> 18/ Caucasian/ Nulliparous	Day 97	13 days	Drug withdrawn	Recovered, Resolved
<u>A46796 /130221/</u> 27/ Caucasian/ Parous	Day 571	2 days	Drug withdrawn	Recovered, Resolved
<u>A52238 /230303/</u> 20/ Caucasian/ Nulliparous	Day 519	4 days	Drug withdrawn	Recovered, Resolved

Source: Summary of Clinical Safety, Page 85, Table 2-29

Medical Reviewer's Comment

- *As noted from the pooled data, a total of 4 ectopic pregnancies occurred in LCS12 group. Two of these subjects were nulliparous and two were parous. None of these 4 ectopic pregnancies ruptured. All were assessed by the investigator as drug-related except for Subject 230303. This patient had a bicornuate uterus, which clearly increases the risk of pregnancy despite intrauterine contraception.*

The frequency of ectopic pregnancy overall and by various subgroups in the pooled dataset is shown in Table 34 below.

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Table 34 Number and Overall Percent of Subjects with Ectopic Pregnancy, Pooled Data

Time of Event	LCS12	LCS16	Mirena
	Pregnancies/Subjects	Pregnancies/Subjects	Pregnancies/Subjects
Year 1	2/1672 (0.1%)	2/1697 (0.1%)	0/256
Year 2	2/1381 (0.1%)	3/1418 (0.2%)	0/220
Year 3	0/1150	4/1201 (0.3%)	0/193
Total 3-Year	4/1672 (0.2%)	9/1697 (0.5%)	0/256
Parity			
Nulliparous	2/608 (0.3%)	4/623 (0.6%)	0/59
Parous	2/1064 (0.2%)	5/1074 (0.5%)	0/197
Age			
18-25 years	2/604 (0.3%)	2/598 (0.3%)	0/40
26-35 years	2/982 (0.2%)	6/1022 (0.6%)	0/136
> 35 years	0/86	1/77 (1.3%)	0/80
BMI			
≤ 30 kg/m ²	4/1409 (0.3%)	7/1417 (0.5%)	0/231
> 30 kg/m ²	0/262	2/276 (0.7%)	0/25

Source: Adapted from Summary of Clinical Safety, Page 86, Table 2-30

In order to account for time at risk for pregnancy (rather than just a rate per number of subjects), the overall risk of ectopic pregnancy by study and pooled data was evaluated by calculating a PI as shown in Table 35.

Table 35 Ectopic Pregnancy Rates per Study and Pooled Data

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

*PI = Pearl Index = ectopic pregnancies occurring per 100 woman-years

Source: Summary of Clinical Safety, Page 84, Table 2-27.

Medical Reviewer's Comment

- *Ectopic pregnancy rates for both LCS12 and LCS16 are very low and similar to the rates with Mirena. The significance of the higher PI with LCS16 is uncertain.*

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The ectopic pregnancy rates associated with LCS12 were further analyzed by the FDA Statistician. The PI in the pooled dataset at Year 1 was 0.14 (95% CI upper bound of 0.50) and over three years was 0.11 (upper bound 0.28).

The FDA Statistician also calculated the ectopic pregnancy rate (PI) for LCS12 in Study A52238 and in the pooled studies by parity.

Table 36 Ectopic Pregnancy Rates by Parity, LCS12

Time	Parity	# of Pregs	Pearl Index (95% CI)	# of Pregs	Pearl Index (95% CI)
		Study A52238		Pooled Data	
Year 1	Nulliparous	1	0.23 (0.006, 1.25)	1	0.20 (0.005, 1.14)
Year 1	Parous	1	0.13 (0.003, 0.73)	1	0.11 (0.003, 0.59)
Year 3 (Cum)	Nulliparous	2	0.18 (0.02, 0.66)	2	0.17 (0.02, 0.60)
Year 3 (Cum)	Parous	1	0.05 (0.001, 0.29)	2	0.08 (0.01, 0.30)

Source: FDA Statistician

European Review

The Applicant has also submitted a marketing application for LCS12 (Jaydess) in Europe, which is currently under review under a Decentralized Procedure. A Reference Member State (Sweden) and other European Health Authorities, in a preliminary assessment, considered the application not approvable at that stage due to concerns regarding the risk of ectopic pregnancy in nulliparous women. Concern was expressed that the target population for Jaydess specifically included nulliparous women, and that an increase in the ectopic rate in these women may cause tubal damage and impair future fertility. There was also speculation that lowering the dose of LNG may increase the rates of ectopic pregnancies. However, as of December 4, 2012, the Applicant and EMA resolved issues and Jaydess was approved with labeling limiting use by nulliparous women.

Medical Reviewer's Comments

- *Based on the review of the data submitted to the NDA, we made the following determinations regarding the risk of ectopic pregnancy with LCS12:*
 - *The overall incidence of ectopic pregnancy in the LCS12 group was 4 out of a total of 1672 subjects or 0.2%. The incidence rate of ectopic pregnancy in nulliparous subjects was 2 out of 608 or 0.3%. In parous subjects, the incidence rate was 2 out of 1064 subjects or 0.2%. These rates of occurrence are very similar.*
 - *The ectopic rate PI for LCS12 based on the 4 ectopic pregnancies across the two studies was calculated by the FDA statistician to be 0.20 for nullips and 0.11 for parous women at Year 1 and 0.17 for nullips and 0.08 for parous women at Year 3.*
 - *The PIs for ectopic pregnancies are greater in the nulliparous subjects than in the parous subjects for both the first year of use and the cumulative three years of use. However, for both time points, the numbers are small and the confidence intervals overlap. Therefore, based on the pooled studies submitted for review, I cannot conclude that the risk of ectopic is greater in nulliparous subjects.*
 - *The European concerns regarding the increased risk of ectopic pregnancy with LCS12 were based on cross-study comparisons with Mirena. Cross-study comparisons are difficult to make, as the demographics of study populations can vary markedly.*
 - *Based on data from the 2 pivotal studies, the risk of an ectopic pregnancy with this product is very low (0.2%) and is similar to the risk of ectopic with Mirena (0.1%).*
 - *If this product is approved, the risk of ectopic pregnancy will be clearly labeled in W+P.*
 - *Data from the 2 clinical trials submitted for review do not support the speculation that lowering the LNG dose in the IUS may increase the rate of ectopic pregnancy. In a pooled analysis of the two studies submitted, the rate of ectopic pregnancy in the LCS16 group was more than twice that in the LCS12 group.*

7.3.4.2 Infections

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

Pelvic Inflammatory Disease (PID)

The diagnosis of PID was made according to the investigator's clinical assessment. A diagnosis of PID necessitated removal of the IUS, and the woman was considered as

having discontinued the study treatment. Most of the PID reported was serious, moderate to severe in intensity and was assessed to be related to study drug,

In Study A52238, 12 cases of PID were reported (six in the LCS12 arm, and six in the LCS16 arm). A total of 7 of these women (LCS12: 4, LCS16: 3) had an acute salpingo-oophoritis diagnosed and a total of 3 of these women (LCS12: 2, LCS16: 1) a tuboovarian abscess. Six of the 12 cases were reported as SAEs relating to PID (2 in LCS12 and 4 in LCS16). One woman in the LCS12 group with salpingo-oophoritis was not coded as an SAE and one woman with a pelvic infection in the LCS16 group was not coded as an SAE. All women with reported PID recovered.

In Study A46796, two SAEs relating to PID were reported (one the LCS16 arm and one in the Mirena arm). Both cases were rated as severe, requiring surgery; salpingo-oophorectomy in one, and appendectomy and salpingo-oophorectomy in the other. Both women recovered. An additional case of salpingo-oophoritis was reported for the LCS12 group as a non-serious event, which did not meet the protocol-defined criteria for PID and did not lead to study discontinuation. The woman recovered with oral antibiotic treatment and continued in the study.

Table 37 Pelvic Inflammatory Disease, Pooled Data

Study	LCS12 N=1672	LCS16 N=1697	Mirena N=256
A52238	6	6	0
A46796	0	1	1
Pooled	6 (0.4%)	7 (0.4%)	1 (0.4%)

Source: Summary of Clinical Safety, Page 77, Table 2-21

Medical Reviewer's Comments

- *The Incidence of PID with LCS12 is similar to the incidence with Mirena.*
- *The Mirena subject shown in Table 38 (Subject 130222) had a reported SAE of pelvic inflammatory disease. This was only suspected by the investigator. Intraoperatively, a severe inflammation of the right ovary (degenerated cyst) and severe appendicitis were detected. The subject underwent a salpingo-oophorectomy and appendectomy, and the IUS was removed.*

Table 38 Pelvic Inflammatory Disease, Pooled Data

	LCS12 N=1672	LCS16 N=1697	Mirena N=256
Time of Event			
Year 1	3/1672	6/1697	1/256
Year 2	1/1381	0/1418	0/220
Year 3	2/1150	1/1201	0/193
Total 3-Year	6 (0.4%)	7 (0.4%)	1 (0.4%)
Parity			
Nulliparous	0	1	0
Parous	6	6	1
Age			
18-25 years	2	0	0
26-35 years	4	6	0
> 35 years	0	1	1
Ethnicity			
Caucasian	6	7	1
Drug Discontinued			
Yes	5	6	0
No	1	1	1

Source: Adapted from Summary of Clinical Safety, Page 78, Table 2-22

Medical Reviewer's Comments

- *The 0.4% rate of PID is identical among the treatment groups.*
- *Most cases of PID occurred during the first year of treatment and most cases (all cases in the LCS12 arm) occurred in parous women.*
- *The 3 cases of PID which occurred in the first year of treatment in the LCS12 group occurred 13 days, 26 days and 271 days post insertion.*

Endometritis

A total of 12 women (0.8%) in the LCS12 and 11 women (0.8%) in the LCS16 arm in the A52238 study, and three women (1.3%) in the LCS12 arm in study A46796 study were diagnosed with endometritis. These were not considered as suspicious for PID by the investigators based on clinical presentation. No cases of endometritis were serious; most events were moderate in severity, and occurred most frequently in parous women and during the first year of the study in both Study A52238 and Study A46796. A total of 4 of the 26 women (15%) with endometritis were withdrawn from Studies A52238 and A46796 due to this AE.

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Table 39 Endometritis, Parameters, Pooled Data

	LCS12 N=1672	LCS16 N=1697	Mirena N=256
Time of Event			
Year 1	11/1672	9/1697	0/256
Year 2	2/1381	3/1418	1/220
Year 3	2/1150	0/1201	0/193
Total 3-Year	15 (0.9%)	12 (0.7%)	1 (0.4%)
Parity			
Nulliparous	3	4	0
Parous	11	7	1
Age			
18-25 years	1	3	0
26-35 years	10	8	1
> 35 years	3	0	0
Drug Discontinued			
Yes	2	2	0
No	12	9	1

Source: Adapted from Summary of Clinical Safety, Page 78, Table 2-22

Medical Reviewer's Comment

- *Endometritis was more frequent in parous women and also more frequent during the first year of study.*

Reproductive System and Breast Disorders

The most common (reported in 2% or more in any treatment group) reproductive system and breast disorders are presented by preferred term below. The frequency was very low in all treatment groups.

Table 40 Frequency of Reproductive and Breast Disorders, Pooled Data

Condition	LCS12	LCS16	Mirena
	N=1672 (100%) n (%)	N=1697 (100%) n (%)	N=256 (100%) n (%)
Any disorder	804 (13.2%)	895 (52.7%)	144 (56.3%)
Ovarian cyst	207 (12.4%)	328 (19.3%)	64 (25.0%)
Dysmenorrhea	144 (8.6%)	127 (7.5%)	18 (7.0%)
Cervical dysplasia	112 (6.7%)	122 (7.2%)	12 (4.7%)
Pelvic pain	99 (5.9%)	127 (7.5%)	1 (0.4%)
Vaginal hemorrhage	76 (4.5%)	77 (4.5%)	8 (3.1%)
Vaginal discharge	61 (3.6%)	64 (3.8%)	4 (1.6%)
Breast discomfort	56 (3.3%)	59 (3.5%)	62 (24.2%)
Breast pain	56 (3.3%)	78 (4.6%)	27 (10.5%)
Dyspareunia	35 (2.1%)	31 (1.8%)	5 (2.0%)
Breast tenderness	33 (2.0%)	36 (2.1%)	3 (1.2%)
Uterine spasm	33 (2.0%)	41 (2.4%)	1 (0.4%)

Source: Summary of Clinical Safety, Page 87, Table 2-31

Medical Reviewer’s Comments

- *In both studies, the frequency of ovarian cysts reported as AEs increased with increasing dose of LNG.*
- *In addition to the MedDRA preferred term “ovarian cyst,” ovarian cysts were also reported using MedDRA preferred terms “hemorrhagic ovarian cyst,” “ovarian cyst ruptured and “ovarian cyst torsion.” If all these preferred terms were included, the overall frequency of ovarian cysts in the LCS12, LCS16, and Mirena groups was 220 cases (13.2%), 341 cases (20.1%), and 64 cases (25.0%), respectively.*

Table 41 Women with Ovarian Cysts, Pooled Data

MedDRA Preferred Term	LCS12 N=1672 (100%) n (%)	LCS16 N=1697 (100%) n (%)	Mirena N=256 (100%) n (%)
Ovarian cyst	207 (12.4%)	328 (19.3%)	64 (25.0%)
Hemorrhagic ovarian cyst	14 (0.8%)	19 (1.1%)	0
Ovarian cyst ruptured	4 (0.2%)	8 (0.5%)	0
Ovarian cyst torsion	0	1 (<0.1%)	0
Any ovarian cyst*	220 (13.2%)	341 (20.1%)	64 (25.0%)
Serious	4 / 220 (1.8%)	3 / 341 (0.9%)	5 / 64 (7.8%)
Non-serious	216 / 220 (98.2%)	338 / 341 (99.1%)	59 / 64 (92.2%)
Conservative Treatment	1	1	0
Surgery	3	2	5
Study drug discontinued			
Yes			
No	5	7	5
	215	337	59

*Numbers may not sum because a women may have had more than one preferred term listed for a reported AE.

Source: Summary of Clinical Safety, Page 89, Table 2-32

7.3.5 Submission-Specific Primary Safety Concerns

Expulsions

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

Table 42 Number of Subjects with Expulsions, Pooled Data

Number of Subjects	LCS12 N=1665* (100%)	LCS16 N=1690 (100.0%)	Mirena N=254 (100.0%)
IUS partially expelled	25 (1.5%)	32 (1.9%)	5 (2.0%)
IUS totally expelled	29 (1.7%)	19 (1.1%)	0
Partial or total expulsion	54 (3.2%)	51 (3.0%)	5 (2.0%)

*Includes only subjects with successful insertions

Source: Integrated Analysis. Page 486, Table 63

Medical Reviewer's Comments

- *More partial and total expulsions occurred in parous women (4.4%) than in nulliparous women (3.2%) and more occurred in women age 18 to 25 (5.4%)*

than in women ages 26 to 35 (3.4%). The majority of the expulsions (54%) occurred within 1 year post insertion.

- *The 3.2% expulsion rate is similar to the rate of 4.9% reported in the Mirena label.*

Perforation

Only one partial uterine perforation was reported in Study A52238. This was a partial perforation which was diagnosed by ultrasound at the scheduled 2 year visit. The subject was in the LCS16 arm. No perforations were diagnosed in Study A46796.

Medical Reviewer’s Comment

- *In the one uterine partial perforation, the IUS was removed vaginally without complications.*

IUD Insertion Ease and Pain

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

Table 43 Number of Successful Insertions, Pooled Data

Number of Subjects	LCS12 n (%)	LCS16 n (%)	Mirena n (%)
First insertion attempted	1672 (100.0%)	1697 (100.0%)	256 (100.0%)
First IUS insertion completed	1617 (96.7%)	1631 (96.1%)	249 (97.3%)
First IUS insertion not completed	55 (3.3%)	66 (3.9%)	7 (2.7%)
Second insertion attempted	52 (100.0%)	61 (100.0%)	6 (100.0%)
Second IUS insertion completed	48 (92.3%)	59 (96.7%)	5 (83.3%)
Second IUS insertion not completed	4 (7.7%)	2 (3.3%)	1 (16.7%)

Source: Summary of Clinical Safety, Page 118, Table 4-4

The reasons for the failed first insertions in the 55 LCS12 subjects were as follows:

- Malfunction of the inserter in 16 subjects (29.1%)
- IUS came out immediately after the insertion in 15 subjects (27.3%)
- Other reasons in 13 subjects (23.6%)
- Cervix too tight in 4 subjects (7.3%)
- Pain in 3 subjects (5.5%)
- Position of the uterus in 2 subjects (3.6%)
- Inserter became unsterile in 1 subject (1.8%) and small uterus in 1 subject (1.8%)

Medical Reviewer's Comment

- *Possibly because of this number of failed insertions, the Applicant decided to modify the IUS inserter after Study A52238 was complete,* (b) (4)

The insertion procedure itself using the modified inserter is unchanged.

Local anesthesia was used for insertion in 134 women (8%) with nulliparous women receiving local more commonly than parous women. Pre-insertion analgesics were given to 570 women (34.1%).

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

IUD Removal Ease and Pain

In both Studies A52238 and A46796 combined, overall removal of LCS12 was assessed by the investigators as easy in 90.8% of subjects. Parity did not affect the assessment; with approximately equal numbers of easy removals in parous and nulliparous women although nulliparous women experienced more pain with removal than parous women.

Over Studies A52238 and A46796, 80% of the women experienced no or only mild pain on removal of the IUS. Nulliparous women experienced more pain during the removal procedure than parous women.

Return to Fertility

In the phase 2 Study A46796, subjects were asked to complete questionnaires if they became pregnant within 3 months or within 12 months of discontinuing the study. In addition, subjects were contacted by the site personnel at 3 and 12 months after the end of study treatment to record any pregnancies that had taken place after the IUS removal and to collect data on return to fertility.

A total of 29 subjects discontinued the study drug to become pregnant (LCS12: 7; LCS16: 11; and Mirena: 11 subjects). Twenty-five of these women conceived within 12 months of discontinuing therapy (LCS12: 6, LCS16: 8; and Mirena: 11).

Twelve months after the end of the study, 555 subjects were successfully contacted and 38 subjects (including the 25 subjects above) had become pregnant. This included 16 subjects in the LCS12 group, 13 in the LCS16 group and 9 in the Mirena group.

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Medical Reviewer's Comment

- *Based on this limited data, there is no evidence to assume that return to fertility with LCS12 is a significant problem.*

Data to support use of new inserter

Because the proposed to-be-marketed (b) (4) inserter was not used in the phase 2 and phase 3 clinical trials, the Division believed more data was needed to support the safety of this device. On July 24, 2012, the Division submitted a Clinical Information Request to Bayer for an update of all safety data collected in their ongoing studies utilizing this inserter. The specific items in this request and Bayer's responses are listed below.

Bayer's Response to the July 24, 2012 FDA Clinical Information Request

Bayer has updated safety information from 3 ongoing phase 3 studies (Protocols 13362, 13363, and 14371) that utilized the to-be-marketed LCS12 inserter. Bayer's response covers the reporting interval subsequent to the 4-month Safety Update Report cut-off date of January 31, 2012 through July 20, 2012. The responses are tabulated by protocol.

Medical Reviewer's Comment

- *A review of the 4-month Safety Update Report can be found in Section 7.7.1.*

Division Information Request 1

The Division requested all available data obtained subsequent to the 4-month Safety Update Reporting period ending January 31, 2012 regarding the to-be-marketed inserter. This would include any additional data from Protocol 13362 as well as new data, if available, from Protocols 13363 and 14371, both of which initiated enrollment in September, 2011.

Bayer Response

Three ongoing studies are being performed using the (b) (4) to-be-marketed inserter. Through July 20, 2012, 963 subjects who were randomized to LCS12 had an insertion attempt with the (b) (4) inserter. A total of 800 (83%) of these subjects were nulliparous.

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Table 44 LCS12 ^{(b) (4)} Insertions

Protocol #	LCS12 Subjects N	Nulliparous Subjects n (%)	First insertion successful n (%)	Reasons for Malfunction	Second insertion Successful/ Failed
13362 (Phase 3 study comparing LCS12 to Yasmin)	279	216 (77)	276 (99)	-IUS did not release from tube -slider problem -strings stuck to scissors	3 / 0
13363 (Phase 3 study comparing LCS12 to Nexplanon)	381	288 (76)	375 (98)	-uterine position --pain -expelled after insertion -device problem, stenotic os	3 / 1 (stenotic os)
14371 (Single arm phase 3 adolescent study)	303	296 (98)	297 (98)	-stenotic os, -pain -expelled after insertion, strings -stuck to scissors	6 / 0

Source: Bayer response to clinical information request

Deaths

Two deaths were reported during the reporting interval in the LCS12 groups.

- Subject 360030028 In Norway in Protocol 13363 had a medical history of “hyperthyreosis.” No information regarding the cause of death was available from Statistics Norway. The information will be obtained from the local police department.
- Subject 440010007, an Austrian subject in Protocol 14371 died in a motor vehicle accident.

Medical Reviewer’s Comment

- *It seems unlikely that either of these deaths were drug-related.*

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Table 45 Drug-Related SAEs and Pregnancies for LCS12 Subjects

Protocol #	LCS12 Subjects N	Study Drug Related SAEs n (%)	Discontinuations due to SAEs n (%)
13362	279	3 (1) -One ectopic pregnancy -One spontaneous abortion -One hemorrhagic ovarian cyst	3 (1)
13363	381	1 (0.3) -One ectopic pregnancy	1 (0.3)
14371	303	3 (1.0) -No pregnancies -Endometritis -Ovarian cyst -Salpingo-oophoritis	2 (0.7)

Source: Bayer response to clinical information request

Table 46 Adverse Events Summary

Protocol #	LCS12 Subjects N	Protocol-Required Procedure-Related AEs* n (%)	Study Drug Related AEs n (%)	Discontinuations Due to AEs n (%)
13362	279	24 (9)	88 (32)	27 (10)
13363	381	80 (21)	193 (51)	33 (9)
14371	303	55 (18)	96 (32)	17 (6)

* Adverse events assessed by the investigator as related to protocol-required procedures but not drug related.

Source: Bayer response to clinical information request

Division Information Request 2

In addition, all available data regarding IUD-related complication rates using the new inserter, such as expulsions, perforations, endometritis, pelvic inflammatory disease, pregnancies and ectopic pregnancy should be submitted from all on-going studies. All collected data regarding the to-be-marketed IUS complications should be stratified by

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parity and all of the data should be compared to rates obtained in the primary study A52238.

Bayer Response

Bayer has submitted data on AEs of interest relating to subject parity, total; and partial expulsions and infections in the LCS12 groups.

Table 47 LCS12 Expulsions and Infections

Protocol # LCS12 Subjects N (%)	Expulsions	Infections
13362 279 (100)	None	-1 subject with endometritis 1 month post insertion
13363 381 (100)	<u>3 expulsions</u> -all within 1 month of insertion	-1 subject with salpingitis 5 months post insertion
14371 303 (100)	<u>6 expulsions</u> -3 within 1 month of insertion -1 was 3½ months post-insertion -2 expulsions are currently being investigated	-3 subjects with endometritis -1 subject with salpingo-oophoritis

Source: Bayer response to clinical information request

Medical Reviewer's Comment

- *Of the 9 partial or total expulsions in the three ongoing studies, 8 occurred in nulliparous subjects and one in a parous subject.*

Table 48 Comparison to Pivotal Study, Pooled Data (A52238 and A46796)

	Pooled Data N = 1672 (100%)	Protocols 13362, 13363, and 14371 N = 963 (100%)
Subjects with successful LCS12 insertions	1665 (99.6%)	960 (99.9%)
IUS partial or total expulsion	54 (3.2%)	9 (0.5%)

Source: Bayer response to clinical information request

Medical Reviewer's Comment

- *Based on the recent studies using the (b) (4) inserter, the rate of successful insertions is equivalent to that with the phase 3 inserter, and the rate of expulsion*

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appears slightly lower, although this may reflect the shorter follow-up time in the three studies.

Division Information Request 3

The Division requested that Bayer provide narrative summary data for study subjects in Study 13362 who underwent sonograms to verify appropriate intrauterine placement of the LCS. This should include (1) the criteria for "investigator discretion" to do a sonogram and (2) percentage of study subjects at these sites who had placement sonograms vs. those who did not.

Bayer Response

Protocol 13362 includes routine post-insertion ultrasound examinations only in subjects randomized to LCS12 in Germany and Austria. In the other countries, post-insertion sonography was not routinely performed. The ultrasound exams done in Germany and Austria were done primarily to obtain information on the silver ring rather than to confirm IUS placement. The number of subjects in Study 13362 with post-insertion sonograms total 279. A total of 185 of the 279 subjects with successful LCS12 insertions (66%) have a specific IUS location noted on the sonogram report.

Medical Reviewer's Comments

- *The data on intrauterine placement are limited because this apparently was not the objective of the ultrasound examination. It is likely that the 66% rate of intrauterine insertion is so low because for other subjects the report did not mention the IUS location, not because the IUS was extra-uterine.*
- *The data submitted by Bayer from the ongoing trials are reassuring regarding the safety and efficacy of the (b) (4) inserter. The data do not provide any evidence that this inserter is less effective or less safe than the inserter used in the phase 2 and phase 3 clinical trials.*

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The most frequently reported AEs were reported using MedDRA (version 14.0).

Table 49 Adverse Event Profile, Pooled Data

	Study A52238		Study A46796		
	LCS12 n (%)	LCS16 n (%)	LCS12 n (%)	LCS16 n (%)	Mirena n (%)
Total no. (%) of women	1432 (100%)	1452 (100%)	240 (100%)	245 (100%)	256 (100%)
Any AE no. (%) women]	1194 (83.4%)	1246 (85.8%)	208 (86.7%)	220 (89.8%)	233 (91.0%)
Drug-related	710 (49.6%)	756 (52.1%)	162 (67.5%)	163 (66.5%)	184 (71.9%)
Maximum intensity					
mild	313 (21.9%)	353 (24.3%)	53 (22.1%)	60 (24.5%)	51 (19.9%)
moderate	616 (43.0%)	633 (43.6%)	122(50.8%)	121(49.4%)	145(56.6%)
severe	261 (18.2%)	250 (17.2%)	33 (13.8%)	37 (15.1%)	36 (14.1%)

Source: Integrated Analysis, Table 209, Table 222

The higher frequency of certain AEs in Study A46796 as compared to Study A52238 (including acne, headache, breast pain and discomfort, mood changes and weight gain) can be explained by the fact that in Study A46796, certain events (including acne, bloating, breast pain, breast tension, edema, headache, mood changes, nausea and weight gain) were classified as progestin-related side effects and assessed at every visit via specific questioning. In contrast, these events were recorded as reported voluntarily by the women in Study A52238. This difference in AE reporting between the two studies may have accounted for the discrepancy between the frequencies of these progestin-related side effects in the two studies.

Medical Reviewer’s Comment

- *The progestin-related side effects could either have been over-reported in Study A46796 as the Applicant contends or these side effects could have been under-reported in Study A52238.*

In the pooled data, drug-related adverse events occurred in 872 (52.2%) subjects in the LCS12 group. The most common drug-related AEs in this group were acne (12.3%), ovarian cyst (7.4%), dysmenorrhea (6.6%), headache (4.5%), vaginal hemorrhage (4.5%), pelvic pain (4.2%), abdominal pain (3.6%) and weight gain (3.6%).

Table 50 Most Frequent Adverse Events, Pooled Data

Adverse Event	LCS12 N=1672 n (%)
Most Frequent Adverse Events	
Any AE	1402 (83.9)
Acne	227 (13.6%)
Ovarian cyst	207 (12.4%)
Headache	196 (11.7%)
Urinary tract infection	180 (10.8%)
Dysmenorrhea	144 (8.6%)
Abdominal pain	119 (7.1%)
Nasopharyngitis	117 (7.0%)
Vaginitis bacterial	117 (7.0%)
Cervical dysplasia	112 (6.7%)
Vulvovaginal mycotic infection	107 (6.4%)
Most Frequent Drug-Related Adverse Events	
Any drug-related AE	872 (52.2)
Acne	206 (12.3%)
Ovarian cyst	124 (7.4%)
Dysmenorrhea	110 (6.6%)
Headache	75 (4.5%)
Vaginal hemorrhage	75 (4.5%)
Pelvic pain	70 (4.2%)
Abdominal pain	61 (3.6%)
Weight increased	61 (3.6%)
Breast discomfort	50 (3.0%)
Mood altered	46 (2.8%)

Source: Summary of Clinical Safety, Page 56, Table 2-9

7.4.2 Laboratory Findings

In both Studies A52238 and A46796, most women had a value within normal limits for each laboratory test. The results of general safety laboratory evaluations for LCS12, including serum chemistry, liver enzymes, lipids, hematology and urinalysis were generally unaffected by treatment with LCS12.

7.4.3 Vital Signs

In both Studies A52238 and A46796, vital signs were analyzed and at screening, Month 12, Month 24 and end of study (Month 36), including weight, systolic and diastolic blood pressure, and heart rate.

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Table 51 Mean Change from Baseline to end of study—Body Weight and Vital Signs – Pooled Data

	LCS12 N=1672 (100%)		Mirena N=256 (100%)	
	Mean Change	(SD)	Mean Change	(SD)
Body weight (kg)	0.56	(5.79)	1.44	(5.03)
Systolic blood pressure (mmHg)	0.0	(12.0)	-2.0	(11.9)
Diastolic blood pressure (mmHg)	-0.3	(8.5)	0.3	(8.0)
Heart rate (beats/minute)	0.0 (10.6)	(10.6)	-0.2	(10.0)

Source: Summary of Clinical Safety, Page 113, Table 4-1

7.4.4 Electrocardiograms (ECGs)

Electrocardiograms were not performed for either Study A52238 or Study A46796.

7.4.5 Special Safety Studies/Clinical Trials

No special safety studies were performed for this submission.

7.4.6 Immunogenicity

Not applicable for this submission.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

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

7.5.2 Time Dependency for Adverse Events

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

7.5.3 Drug-Demographic Interactions

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

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7.5.4 Drug-Disease Interactions

No drug-disease interactions were studied.

7.5.5 Drug-Drug Interactions

No drug-drug interaction studies were performed for this NDA application. Class labeling for progestins includes a section on drug-drug interactions, which will be included in the LCS12 label.

7.5.6 Bone Mineral Density

Bone mineral density was measured at the lumbar spine using DXA in a subgroup of 205 women (LCS12, 102 women; LCS16, 103 women) in Study A52238 only. Baseline measurements were compared with measurements at Month 12, Month 24 and End of Study or premature discontinuation. Percentage changes were calculated. There was a slight increase in mean BMD at both anatomic sites at all three post-baseline visits in both treatment groups. For the LCS12 treatment group, the mean BMD increase in the lumbar spine was 0.02% and in the total hip was 0.01%.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

No human carcinogenicity trials were indicated or performed.

7.6.2 Human Reproduction and Pregnancy Data

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

Medical Reviewer's Comments

- *LNG is transferred to the infants' circulation via the breast milk; this is noted in labeling for Mirena and other LNG contraceptives, and will be labeled for Skyla.*
- *In general, no adverse effects have been found from the small amounts of progestins that pass into the breast milk of nursing mothers.*

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7.6.3 Pediatrics and Assessment of Effects on Growth

No effect on growth or development has been observed in infants' breast fed by users of 20 µg/day LNG-IUS, compared with infants of copper IUD users.

7.6.3.1 Pediatric Research Equity Act (PREA)

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

Based on the intended use of the product, Bayer proposed to address the PREA requirements for LCS12 as follows:

- Because contraception is not needed and LCS12 will not be indicated in pre-menarchal patients, Bayer requested a partial waiver from pediatric study requirements for these patients.
- Because the reproductive physiology of post-pubertal adolescent females less than 17 years of age is similar to that of other women of reproductive age, Bayer requested that the PREA requirements for post-menarchal pediatric patients be deemed fulfilled by extrapolation of adult data.

The Division agreed with Bayer's requests and met with the Pediatric Review Committee (PeRC) on August 15, 2012.

Medical Reviewer's Comments

- *The Division's recommendations regarding the partial waiver for premenarchal girls and data extrapolation from adult to postpubertal females was accepted by the PeRC. No PREA postmarketing requirement will be needed for this submission*
- *As discussed in Section 7.7.1.6 of this review, Bayer is currently conducting a phase 3b trial in adolescent women in Europe to investigate the safety of LCS12 in users between menarche and the age of 18 (Protocol 14371). The study is being conducted in accordance with the Pediatric Investigation Plan as approved by the EMA's Pediatric Committee. The study will enroll 300 women and is focusing on the assessment of AEs, bleeding patterns, discontinuation rates, ease and pain of insertions and removals, expulsion risks and adequate counseling in the adolescent population. The treatment duration is one year with an option to continue LCS12 use and observation in the study up to three years. The PeRC recommended that we request the data obtained from the completed study to support the safety profile of LCS12 in adolescent women.*

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7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Not applicable for this submission.

7.7 Additional Submissions / Safety Issues

7.7.1 The 4-Month Safety Update Report

A 4-Month Safety Update Report (PSUR) was received on April 5, 2012 and covered the period from September 1, 2011 to January 31, 2012.

This report includes safety information obtained during the reporting interval from 5 ongoing LCS clinical trials (Protocols 310442 [extension phase of Study A52238], 91775, 13362, 13363, and 14371). Three of these studies (Protocols 13362, 13363, and 14371) are being performed using the modified (b) (4) IUS inserter, which is of the same design as will be used for the marketed product. See Appendix 2.

No deaths were reported during the reporting period from September 1, 2011 to January 31, 2012.

7.7.1.2 Protocol 310442 (Extension phase of the primary study A52238)

This extension phase was limited to LCS16 users only. Safety information was obtained from 650 WY of exposure in this group. Two SAEs were reported.

- Subject 120629 was a 24 year old Caucasian woman who had a uterine perforation.
- Subject 24437 had an episode of severe depression.

7.7.1.3 Protocol 91775

This is a phase 3, multicenter, open-label, single arm study evaluating the efficacy, safety, and pharmacokinetics of LCS12 for up to 3 years in women 18 to 40 years of age in China, Korea and Australia. Safety information was obtained from 1640 WY of exposure to LCS12.

The most frequently (i.e., more than 5% in LCS12-treated women) reported AEs by MedDRA preferred term were:

- Nasopharyngitis in 62 women (6.7%)
- Upper respiratory tract infection in 186 women (20.1%)
- Vulvovaginal candidiasis in 48 women (5.2%)
- Headache in 54 women (5.8%)
- Ovarian cyst in 139 women (15.0%)
- Uterine cervical erosion in 52 women (5.6%)

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- Vaginal hemorrhage in 69 women (7.5%)

Serious adverse events in this study are listed below.

Table 52 LCS12 SAEs, September 1, 2011 to January 31, 2012, Protocol 91775

Subject no.	Age Ethnicity	LCS12 insertion date	Event as reported/ Onset of the event	Causality assessment by: Investigator/ Sponsor
540090040	29 Asian	2/5/2010	Ovarian pregnancy 1/12/2012	Related/ Related
540090024	37 Asian	10/15/2009	Acute bronchitis 8/22/2011	Unrelated/ Unrelated
400010018	20 Caucasian	9/17/2009	Endometriosis 11/17/2011	Unrelated/ Unrelated
540060004	34 Asian	11/18/2009	Hepatic cyst 10/20/2011	Unrelated/ Unrelated
560010014	42 Asian	3/5/2010	Breast cancer Onset not reported	Unrelated/ Unrelated
560030007	32 Asian	12/31/2009	Upper respiratory tract infection with fever 10/25/11	Unrelated/ Unrelated
540160035	31 Asian	7/23/2009	Rupture of the corpus luteum 11/24/2011	Related/ Related
560020009	33 Asian	2/3/2010	Acute tonsillitis 10/26/11	Unrelated/ Unrelated

Source: 4-Month Safety Update Report, Page 12, Table 3

Medical Reviewer's Comments

- *I am in agreement with the both the investigator's and the Applicant's causality assessments.*
- *Subject ID 540090040) was a 28 year old Chinese female who was diagnosed with an ectopic (left ovarian) pregnancy on January 12, 2012 during the second treatment year. The subject's last menstrual period was November 30, 2011. She complained of abdominal pain and had a positive pregnancy test. She was hospitalized and underwent a left oophorectomy.*

7.7.1.4 Protocol 13362 (Study A57046)

This is a phase 3b, multicenter, randomized, open-label, study, conducted in Austria, Belgium, Germany, and the US. The study began in January 2011. The study objective is to evaluate user satisfaction during use of LCS12 in comparison to the combined oral contraceptive Yasmin (0.03 mg ethinyl estradiol/3 mg drospirenone) in young (18 to 29 years) nulliparous and parous women over 18 months of use. Secondary objectives

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include evaluation of tolerability and bleeding patterns over 18 months of use. Women in the LCS12 arm will be able to continue treatment for the full intended 3 year duration of use.

A total of 645 subjects were screened, of which 78 were screen failures and 567 were randomized, approximately 1:1 as follows: 282 subjects to LCS12 and 285 subjects to Yasmin. Of the 282 LCS12 subjects randomized to LCS, 279 had an insertion attempt and 3 LCS12 subjects discontinued the study and did not have an insertion attempt.

The mean age for LCS12 subjects in this study was 23.8 years (SD – 3.0 yrs) and 216 (77.4%) of these subjects were nulliparous subjects. All 279 subjects had successful LCS12 insertions; however, 3 (1.1%) of the subjects required a second insertion attempt.

This trial was the first study to use only the modified IUS inserter design that is proposed for use with Skyla, and an interim analysis was provided for in the protocol to evaluate insertion-related information. The interim analysis was done after all LCS insertions and the associated 1 month follow up visits had been completed.

Ultrasound was performed after insertion in a subset of subjects in Austria and Germany at the discretion of the investigator. Data on ultrasound exams was not planned to be included in the interim study report. However, the Applicant states that data on file demonstrated that, as of May 22, 2012, a total of 182 subjects in the LCS12 arm underwent at least one ultrasound exam following LCS12 insertion (159 on the same day as the insertion or within the period between the insertion and the 1 month follow up, the remainder done some time after the 1 month follow up). The Applicant states that, in all cases, proper intrauterine placement was confirmed.

Safety information was obtained from 220 WY of exposure to LCS12 in this study.

The most frequent (i.e., more than 5% the LCS12 treatment group) were:

- Abdominal pain in 18 women (6.5%)
- Headache in 17 women (6.1%)
- Dysmenorrhea in 30 women (10.8%)
- Ovarian cyst in 14 women (5.0%)
- Acne in 14 women (5.0%)

A total of 4 SAEs were reported as of January 31, 2012. These were cervical dysplasia, malignant melanoma, a cruciate ligament injury to the right knee and a case of appendicitis. None of these events were deemed causally related to LCS12 by either the Applicant or the investigator.

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The interim report covered up to May 22, 2012. This report contained two on-treatment pregnancies (one ectopic) and 1 ovarian cyst in the LCS12 arm.

Medical Reviewer's Comments

- *The analysis was completed and the results were reported in the study report for Protocol 13362, which was finalized January, 2012. The report was submitted under IND 73,505 (S-0060) on March 27, 2012. It describes the baseline characteristics, insertion data and the associated follow up through study visit 3 (1 month post-insertion) for LCS12 subjects only.*
- *On July 24, 2012, the Division requested further information from this study regarding the to-be-marketed inserter. Bayer responded to the request with an update on the use of the inserter in 3 ongoing clinical phase 3 trials (see Section 7.3.5). This information request resulted in a major amendment and a 3-month extension of the PDUFA goal date.*

7.7.1.5 Protocol 13363

This is a phase 3b multicenter, open-label, randomized, controlled parallel-group study, with study sites in Australia, Finland, France, Norway, Sweden, and the United Kingdom, which was initiated in September 2011 and used the (b) (4) inserter. This study assesses discontinuation rates (primary objective), bleeding patterns, user satisfaction and the AE profile of LCS12 in comparison to an etonogestrel subdermal implant over 12 months in women 18 to 35 years of age. Women in the LCS12 arm are able to continue treatment for the full intended 3 year duration of use.

The most frequently (i.e., more than 5% in the LCS12 treatment group) reported AEs by MedDRA preferred term were as follows:

- Procedural pain in 29 women (10.5%)
- Dysmenorrhea in 28 women (10.2%)
- Uterine spasm in 41 women (14.9%)

Three SAEs have been reported (2 subjects with pneumonia and 1 subject with a herniated disk). None of these events were deemed causally related to LCS12 by the Applicant or the investigator.

Medical Reviewer's Comment

- *Updated information from this study regarding the to-be-marketed inserter was also included in the Clinical Information Request of July 24, 2012.*

7.7.1.6 Protocol 14371

This study is a phase 3b study that was initiated in Europe in September 2011 in adolescent women to investigate the safety of LCS12 in users between menarche and the age of 18. The study plans to enroll a total of 300 women and focuses on the assessment of AEs, bleeding pattern, discontinuation rate, ease and pain of insertion

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and removal, expulsion risk and adequate counseling in the adolescent population. The treatment duration is one year with an option to continue LCS12 use and observation in the study up to three years.

The most frequently (i.e., more than 5% in the LCS12 treatment group) reported AEs as of December 31, 2011 were:

- Abdominal pain in 12 women (10.7%)
- Abdominal pain, lower in 6 women (5.4%)

There were no on-treatment SAEs, SAEs related to insertion attempts, or pregnancies reported for this study during the reporting period.

Medical Reviewer's Comments

- *This study uses the to-be-marketed (b) (4) inserter, which is further discussed in Section 7.3.5.5.*
- *This study is being conducted in accordance with the Pediatric Investigation Plan as approved by the European Medicines Agency Pediatric Committee.*
- *Updated information from this study regarding the to-be-marketed inserter was also included in the Clinical Information Request of July 24, 2012.*

7.7.1.7 Extent of Additional Exposure

As of the cutoff date of 31 Jan 2012, the estimated additional exposure accumulated for LCS12 and LCS16 is shown in Table

Table 53 Total Exposure, LCS12 and LCS16

	LCS12 Exposure (WY)	LCS16 Exposure (WY)
NDA Exposure	3820.65	3965.33
Ongoing Trials	1860	1860
Total	5680.65	4614.33

Source: Medical reviewer

Medical Reviewer's Comment

- *The submitted PSUR covering the period from September 1, 2011 to January 31, 2012 does not document any unexpected safety findings for LCS12. However, there was some concern in the EU regarding the frequency of ectopic pregnancy in nulliparous women (See Section 7.3.4.1 for a discussion of this issue.)*

8 Postmarket Experience

No commercial marketing experience has been obtained for LCS12 because this product has not yet been marketed in any country.

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Marketing applications for LCS12 were submitted in Europe in parallel with the submission of this NDA. On March 2, 2012, Bayer was notified by the Swedish health authority (acting as the reference member state for the EU) that LCS12 was not approvable due to the risk of ectopic pregnancy especially in nulliparous women. Sweden noted that although the absolute risk of ectopic pregnancy is low, it may be higher than the rate with Mirena. Also since the product may appeal to younger nulliparous women, an ectopic pregnancy may impair future fertility. For a further discussion of this issue, see Section 7.3.4.1.

The Applicant considers the comparison to the historical Mirena data to be of limited value and states that even if comparisons are made, the CIs of the PIs for both products are overlapping and therefore no conclusions can be drawn regarding contraceptive efficacy or relative risks of ectopic pregnancy.

(b) (4)

Medical Reviewer's Comment

- *On December 4, 2012, the Health Authorities of the EU Member States granted Bayer marketing approval for Jaydess. Because of the EU concern regarding the increased risk for ectopic pregnancy compared to Mirena, the Applicant agreed to not specifically target nulliparous patients for Jaydess and agreed to remove the sentence [REDACTED] (b) (4) from the indication. Language indicating that Jaydess is not first-line contraception for nulliparous women was added to the Warnings section.*

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9 Appendices

Appendix 1: Schedule of Assessments, Study A55238

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

Appendix 2: Overview of Ongoing Phase 3 Clinical Studies with LCS

Protocol Phase No. Centers: Location	Design Duration	Study population	No. of women by treatment group Study Period	Main outcomes
310442 -Extension Phase for LCS16 only -108 Centers: Europe, US, Canada, South America	-Multicenter, randomized, open label, -2-arm -3 years up to 5 years -LCS16 only	-Healthy, 18-35 yrs -nulliparous or parous	-LCS16 only: 707 -FPFV ² : 8/23/10	-Pregnancy rate -Bleeding pattern -Safety
91775 -25 centers: China (18), Korea (5), Australia (4)	-Multi-center, open label, -single-arm -3 Year -LCS12 only	-Healthy, 18-40 yrs -nulliparous or parous	-LCS12: 924 -FPFV: 4/09/09	-Pregnancy rate -Bleeding pattern -Safety -Pharmacokinetics
13362 -42 centers: Austria (10), Belgium (5), Germany (15), USA (12)	-Multicenter, open label, -2-arm -18 months; possible extension up to 3 years - (b) (4) inserter ¹	-Healthy, 18-29 yrs -nulliparous or parous with regular menses	-LCS12: 282 -Yasmin: 285 -FPFV: 1/6/11	-User satisfaction -Pearl Index -Tolerability -Bleeding pattern -Safety
13363 -43 centers: Australia (6), Finland (10), France (6), Norway (5), Sweden (11), UK (5)	-Multicenter, open Label -2-arm -12 months, with an extension for up to 3 years - (b) (4) inserter ¹	-Healthy, 18-35 yrs -nulliparous or parous	-LCS12: 380 planned -Nexplanon: 380 planned -FPFV: 9/15/11	-Discontinuation rate -Pearl Index -User satisfaction -Bleeding patterns -Safety
14371 -39 centers: Austria (5) Belgium (5) Denmark (3) Finland (5) Germany (9) Netherlands (7) Norway (2) Sweden (3)	-Multicenter, open label, single-arm -12 months, with an extension for up to 3 years - (b) (4) inserter ¹	-Healthy, menarche to 18 yrs -nulliparous or parous adolescents with regular menses	-LCS12: 300 planned -FPFV: 9/26/11	-Adverse Events -Pregnancy rate -User satisfaction -Tolerability -Safety -Pharmacokinetics

¹ These studies (protocols 13362, 13363, and 14371) are being performed using the modified IUS inserter (b) (4) inserter), which is of the same design as will be used for the marketed product.

First patient, first visit

Source: 4-Month Safety Update Report, Page 7, Table 1

Clinical Review
Ronald J. Orleans, M.D.
NDA 203159
Skyla® (levonorgestrel-releasing intrauterine system)

9.1 Literature Review/References

Gemzell-Danielsson K. A randomized, phase II study describing the efficacy, bleeding profile, and safety of two low-dose levonorgestrel-releasing intrauterine contraceptive systems and Mirena Fertil Steril 2012:97616-22

Medical Reviewer's Comment

- *This article reports on the findings of the phase 2 study A46796.*

9.2 Labeling Recommendation

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

9.3 Advisory Committee Meeting

No Advisory Committee Meeting was indicated or held.

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

/s/

RONALD J ORLEANS
12/26/2012

LISA M SOULE
12/27/2012

I concur with Dr. Orleans' recommendation that NDA 203-159 be approved for prevention of pregnancy for three years.

CLINICAL FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 203159 **Applicant: Bayer Healthcare** **Stamp Date: December 9, 2011**

Drug Name: Skyla® **NDA Type: 505(b)(1)** **PDUFA Date: October 9, 2012**
Levonorgestrel-releasing **Standard Review**
intrauterine system

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			electronic CTD with Global Summit Review enabled
2.	On its face, is the clinical section of the application organized in a manner to allow substantive review to begin?	X			Well organized
3.	Is the clinical section of the application indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?	X			
5.	Are all documents submitted in English, or are English translations provided when necessary?	X			
6.	On its face, is the clinical section of the application legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted draft labeling in electronic format consistent with 21 CFR 201.56 ¹ and 201.57 (or 21 CFR Subpart C for OTC products), current divisional and Center policies, and the design of the development package?	X			PLR labeling submitted in Module 1.14
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?	X			Clinical efficacy and safety summaries are submitted.
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			Submitted in the Clinical Overview (Section 2.5)
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?			X	Application filed as a 505(b)(1)
DOSE					
13.	If needed, has the sponsor made an appropriate attempt to determine the correct dosage and schedule for this product (i.e., appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Arms: Location in submission:	X			
EFFICACY					
14.	On its face, do there appear to be the requisite number of	X			

¹ http://www.access.gpo.gov/nara/cfr/waisidx_01/21cfr201_01.html

CLINICAL FILING CHECKLIST FOR A NEW NDA/BLA

	Content Parameter	Yes	No	NA	Comment
	adequate and well-controlled studies in the application? Pivotal Study: Phase 3 Primary Study A52238 Protocol 91665 Indication: Prevention of pregnancy for up to 3 years Study #2: Phase 2 Study A46796 Protocol 91412 Indication: Prevention of pregnancy for up to 3 years				
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?			X	
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure ²) been exposed at the dose (or dose range) believed to be efficacious?	X			
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the sponsor submitted the coding dictionary ³ used for mapping investigator verbatim terms to preferred terms?	X			Section 1.14.1.5
24.	Has the sponsor adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					

² For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

³ The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

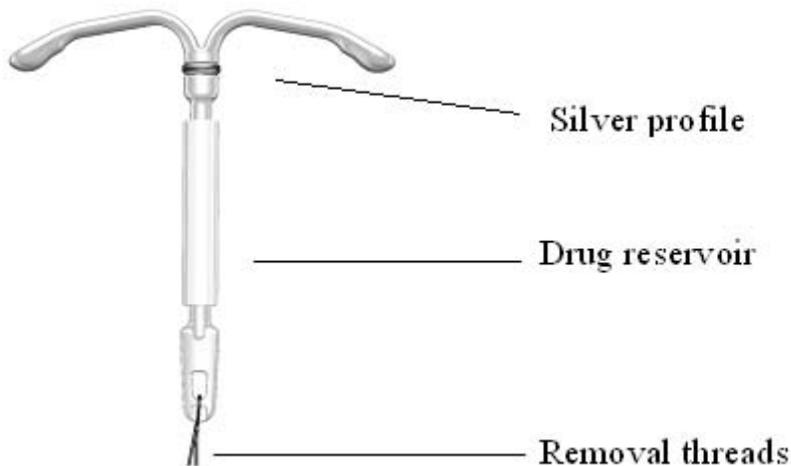
CLINICAL FILING CHECKLIST FOR A NEW NDA/BLA

	Content Parameter	Yes	No	NA	Comment
26.	Has the applicant submitted all special studies/data requested by the Division during the pre-submission discussions with the sponsor?	X			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	Not needed for this application
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			Statistical Analysis submitted in Section 5.3.5.3
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			
CONCLUSION					
40.	From a clinical perspective, is this application fileable? If not, please state why.	X			

CLINICAL FILING CHECKLIST FOR A NEW NDA/BLA

This NDA is for a proposed low dose progestin IUD “Skyla” or “LCS12 low-dose levonorgestrel intrauterine contraceptive system.”

- So called because the *in vitro* release rate of 12 µg/24 hours.
- Seeking indication for prevention of pregnancy for up to 3 years.
- Mirena has an initial *in vitro* release rate of 20 µg/24 hours. Mirena can be used for up to five years. Skyla has a lower daily release rate of LNG and a smaller insertion tube diameter than Mirena and Bayer believes it may be easier to use in nulliparous patients.



- The drug reservoir consists of (1) the inner stem (2) a drug core, and (3) a covering outer membrane
- A silver ring is added around the vertical stem of the T-frame to facilitate detection and aid in differentiation of LCS12 from other intrauterine systems during ultrasound examination.

CLINICAL FILING CHECKLIST FOR A NEW NDA/BLA

The NDA consist of 2 studies:

Study	Design	Study population	Number of women by treatment group	Main outcomes
<p style="text-align: center;"><u>Phase 3</u></p> <p>-A52238 Protocol 310442</p> <p>-IND 73,505</p> <p>-11 countries (Europe, US, Canada, South America)</p> <p>-2007-2011</p>	<p>-Multicenter, randomized, open label, 2-arm, parallel group</p> <p>-3 years (up to 5 years for LCS16 only)</p>	<p>- Healthy</p> <p><u>-18- to 35 years</u></p> <p>-nulliparous or parous women</p>	<p><u>N=2884</u></p> <p>-LCS12: 1432</p> <p>-LCS16: 1452</p>	<p>-Pregnancy rate</p> <p>-Bleeding pattern</p> <p>-Safety</p>
<p style="text-align: center;"><u>Phase 2</u></p> <p>-A46796 Protocol 308901</p> <p>-5 countries in Europe</p> <p>-2005-2011</p>	<p>-Multicenter, randomized, open label, controlled, 3-arm, parallel Group</p> <p>-3 years</p>	<p>-Healthy</p> <p><u>-21 to 40 years</u></p> <p>-nulliparous or parous women</p>	<p><u>N=741</u></p> <p>-LCS12: 240</p> <p>-LCS16: 245</p> <p>-Mirena: 256</p>	<p>-Pregnancy rate</p> <p>-Bleeding pattern</p> <p>-Safety</p>

- Inclusion and exclusion criteria were similar between the pivotal study A52238 and study A46796. Relevant differences between the two studies are the different inclusion criteria regarding age, i.e., 18 to 35 years in study A52238 compared to 21 to 40 years in study A46796.
- The primary pregnancy rate is based on data from women 18 to 35 years of age during the first year of use (Year 1 PI) and for the total treatment duration of 3 years (3-year PI) in the pivotal study A52238.

Phase 3 Pivotal Study A52238 (Protocol 310442)

- The study was a multicenter, multi-national randomized open label study comparing Skyla with a second LNG IUS with a different LNG load and was conducted in 11 countries in Europe, Latin America, the US and Canada.
- A total of 2884 women with an insertion attempt (FAS).
- Skyla: 1432 generally healthy women aged 18–35 including 38.8 % (556) nulliparous women of whom 83.6% (465) were nulligravid.
- Included 1287 North American women of whom 632 received LCS12 and 655 received LCS16 (LCS12 Year 1 = 534 WY (6900 28-day cycles) and LCS12 Year 3 = 1274 WY (16,000 28-day cycles).
- Per region, the number of women included in the analysis (women who had an LCS insertion attempt) in the Skyla group was as follows: 654 from European countries, 632 from North America and 146 from Latin America. The racial

CLINICAL FILING CHECKLIST FOR A NEW NDA/BLA

demographic of enrolled women was: Caucasian (79.7%), Hispanic (11.5%), Black (5.2%), Asian (0.8%), and Other (2.7%).

Efficacy

- The primary efficacy variable for this study was the pregnancy rate.
- Secondary efficacy variables included assessments of bleeding patterns as recorded in subject-kept diaries.
- The PI was based on pregnancies that occurred after the onset of treatment and within 7 days after IUS removal or expulsion.
- Months that included the use of back-up contraception, but in which conception did not occur, were not included in the calculation of the PI.

Study A52238 (Unadjusted FAS)

PI's	LCS12			LCS16		
	Women/ Pregnancies	WY	PI (Upper Bound of CI)	Women/ Pregnancies	WY	PI (Upper Bound of CI)
Year 1	1432 / 5	1217.78	0.41 (0.96)	1452 / 2	1252.78	0.16 (0.58)
Year 2	1162 / 3	1015.67	0.30 (0.86)	1206 / 4	1067.49	0.37 (0.96)
Year 3	960 / 2	825.17	0.24 (0.88)	1010 / 4	891.09	0.45 (1.15)
3-year PI	1432 / 10	3058.62	0.33 (0.60)	1452 / 10	3211.36	0.31 (0.57)
-Nullip	556 / 4	1110.63	0.36 (0.92)	574 / 3	1205.33	0.25 (0.73)
-Parous	876 / 6	1947.99	0.31 (0.67)	878 / 7	2006.03	0.35 (0.72)

- For Study A52238, for 18- to 35-year old women, the unadjusted PI for LCS12 for the first year was 0.41 with the upper limit of the two-sided 95% CI of 0.96, and 0.33 for the total three years of use, with the upper limit of the two-sided 95% CI of 0.60.

Safety

- There was one death in study A52238, a suicide in a 20 year-old woman related to problems with depression and eating disorder, assessed by the investigator as unrelated to study drug.
- The most frequent AEs causing discontinuation of study drug (total women and in either treatment group) were vaginal hemorrhage, device expulsion, pelvic pain, and acne.

Phase 2 Supportive Study A46796 (Protocol 308901)

- Skylar was compared to LNG16 and to Mirena.
- The FAS included a total of 741: 240 women in the LCS12 group, 245 women in the LCS16 group and 256 women in the Mirena group.
- Pregnancies (N=6)
 - LCS12 = 1
 - LCS16 = 5 (2 ectopic; 2 spontaneous abortion; 1 carried to term)

CLINICAL FILING CHECKLIST FOR A NEW NDA/BLA

Regulatory Issues

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

- Regarding efficacy, the phase 3 trial is the stand-alone pivotal study.
- The pivotal trial contained the required number (10,000) of cycles
- At least 45% of the subjects were from North America
- “During treatment” pregnancies were defined as pregnancies with estimated date of conception after the insertion of LCS12 and within 7 days after removal of Skyla or detection of expulsion.
- The evaluation of efficacy was based on the 12 month and cumulative 3-year unadjusted Pearl Indices for women 18 to 35 years of age from the phase 3 study A52238 (protocol 310442). Unadjusted Pearl Indices for each year of use (e.g., 12 month, 24 month and 36 month) were also submitted.
- The PIs were calculated based on completed 28-day cycle equivalents.
- These PIs were also calculated for subgroups stratified by age, parity, body mass index (BMI)
- Bayer agreed the exposure would be calculated using all completed 28-day cycles in which no back-up contraception was used. Thirteen (13) cycles would constitute 1 woman-year.
- Given that a month in which back-up contraception was used might span two or more 28 day cycles, the Applicant developed an algorithm to assign back-up to a single specific 28-day cycle equivalent in such cases.
- Bayer provided the bleeding data by 28-day reference periods.

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

The Application is fileable.

A possible review issue will be the to-be-marketed inserter used to place Skyla into the endometrial cavity. Skyla is placed in the uterus with a preloaded, ready-to-use inserter. The inserter used in phase 2 and phase 3 studies (A46796 and A52238) was of the same design as that used for the approved Mirena. However, this inserter will not be the to-be-marketed inserter. The to-be-marketed LCS12 inserter was modified to (b) (4)

[REDACTED] The actual insertion procedure itself however will remain unchanged. CMC and CDRH will be consulted to evaluate the impact, if any, on safety and efficacy of the modified inserter.

Reviewing Medical Officer: Ronald J. Orleans, M.D.

Date: February 1, 2012

Clinical Team Leader: Lisa M. Soule, M.D.

Date: February 21, 2012

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

/s/

RONALD J ORLEANS
02/21/2012

LISA M SOULE
02/21/2012

I concur with Dr. Orleans that NDA 203-159 is fileable.