U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA 203-159/0000
Drug Name:	Skyla or LCS12 (13.5 mg levonorgestrel-releasing intrauterine system)
Indication(s):	Prevention of pregnancy for up to 3 Years
Applicant:	Bayer HealthCare Pharmaceuticals, Inc.
Date(s):	Stamp Date: 12/09/2011
	PDUFA Date: 01/09/2013 (Revised date due to extension)
Review Priority:	Original - Standard
Biometrics Division:	Division of Biometrics III
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Keywords:	NDA review, clinical studies, survival analysis, Pearl Index

Table of Contents

LIST OF TABLES

1 EXECUTIVE SUMMARY

From a statistical perspective, this single phase 3 study provides evidence demonstrating the efficacy of LCS12 (13.5 mg levonorgestrel contraceptive intrauterine system) for the prevention of pregnancy for up to 3 years in women 18 to 35 years of age. The Pearl Index at the end of the first year is 0.41 (95% CI is 0.13 to 0.96). Supportive evidence is based on the Kaplan-Meier cumulative pregnancy rate. The cumulative pregnancy rate per 100 women at the end of the first year is 0.39 (95% CI is 0.16 to 0.94) and at the end of the third year is 0.89 (95% CI is 0.48 to 1.66).

There were no major statistical efficacy issues encountered in this review. One minor analysis issue was that the Applicant used exposure based on days to calculate the Pearl Index while the Agency uses exposure based on 28-day cycles. Analyses using exposure based on 28-day cycles were calculated for this review. The Pearl Index results based on either days or 28-day cycles were consistently similar.

2 INTRODUCTION

2.1 Overview

The Applicant, Bayer Healthcare Pharmaceuticals Inc, is seeking approval of LCS12, a 13.5 mg levonorgestrel (LNG)-releasing intrauterine system (IUS), for the prevention of pregnancy for up to 3 years. LCS12 contains the same active ingredient as their currently marketed 5-year 52 mg LNG-releasing IUS, Mirena® but at a lower dose.

To support the safety and efficacy of LCS12, the Applicant conducted a randomized, open-label, phase 3, multinational study A52238 (Protocol 310442). The study design was finalized based on the results from a dose-finding phase 2 study A46796. The study was initiated in 2007 in Europe, North America and South America. The key elements of the phase 3 study design are summarized in Table 1.

Table 1. Summary of Reviewed Study

Study	Phase and Design	# of Subjects per Arm	Study Site [Country (# of sites)]	Treatment Period	Follow-up Period	Study Population
A52238 (Protocol 310442)	Phase 3, 2-arm, randomized, open-label, no-control, multi-center	Planned: 2820 1410 per group Analyzed:2884 LCS12: 1432 LCS16: 1452	Argentina (5), Canada (13), Chile (3), Finland (15), France (8), Hungary (8), Mexico (4), Norway (5), Netherlands (9), Sweden (12), U.S. (56)	3 years for LCS12 5 years for LCS16	Up to 1 year for withdrawals due to a desire for pregnancy; No specification for other follow up	Women aged 18-35 who have regular menstrual cycles (21-35 days) and need contraception

Source: reviewer analysis based on datasets: Rand01 and DEMO01

2.2 Data Sources

The study report and pertinent information were submitted electronically. The dataset quality is acceptable. Analysis datasets and the associated definition files are listed in Table 2.

Table 2. Study A52238: Data Sources

File	Location
Datasets	*\\CDSESUB1\EVSPROD\nda203159\0000\m5\datasets\a52238\analysis\datasets*
Definition Files	*\\CDSESUB1\EVSPROD\nda203159\0000\m5\datasets\a52238\analysis\datasets\define.pdf*

Source: Module 5.3.5.2 in this NDA submission package

2.3 Indication(s)

LCS12 is indicated for the prevention of pregnancy for up to 3 years.

3 STATISTICAL EVALUATION

This section evaluates the study design and the efficacy results of phase 3 study A52238.

3.1 Data and Analysis Quality

To evaluate contraceptive efficacy, all cycles with use of backup contraceptive methods must be excluded from the analysis. The exposure cycles in the Applicant's efficacy dataset EXPOSUA can be partially reproduced from the source dataset after removing those cycles identified as having backup contraceptive method use. The Applicant used World Health Organization (WHO) based drug-code datasets, which were not available to the reviewer, to identify contraceptive drugs that could be used as a backup method. Using on a list of backup contraceptive drugs used for another contraceptive product application, this reviewer created an analysis dataset by excluding cycles where the following backup methods were used:

- Other birth control drugs or condom (based on the analysis datasets MED03)
- Drugs whose medication texts contain "3-OXOANDROSTEN (4) DERIVATIVES", or "PREGNADIEN DERIVATIVES", or "SEX HORMONES", or "ESTROGENS", or "ESTREN", or "CONTRACEPTI", or "PROGESTO" or "GONADOTROPIN" (based on concomitant medication in the analysis datasets MED03)

The primary efficacy results based on the reviewer-created analysis dataset are very similar to those based on the Applicant-submitted analysis dataset. Therefore, this review uses the Applicant-provided datasets for efficacy evaluation.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

Study A52238 was a randomized, open-label, parallel-group, two-arm, multi-center (138 sites), multi-national (11 countries), phase-3 clinical trial in women 18 to 35 years of age desiring contraception. A total of 2820 eligible healthy women was planned to be randomized in a 1:1 ratio (1410 subjects per group) to one of the following two intrauterine treatment groups:

- LCS12 (13.5 mg levonorgestrel)
- LCS16 (19.5 mg levonorgestrel)

The maximum duration of treatment was 3 years for the LCS12 arm and up to 5 years for the LCS16 arm.

During study treatment, subjects were asked about the use of any concomitant contraceptive methods and their use was recorded in the subject diary on a monthly basis. The diary statement to elicit concomitant contraceptive use was as follows: *Contraceptive method was used: Yes or No*. There was no question or prompt asking what kind of contraceptive method was used. The only concomitant contraception allowed was a barrier method, e.g. condoms to prevent sexually transmitted diseases. In addition, concomitant

medication use was recorded separately by the investigator during clinical visits at months 3, 6, 9, 12, 18, 24, and 30 but there was no specific question or prompt for eliciting contraceptive use.

During study treatment, subjects were asked by the investigator at every clinical visit (Months 3, 6, 9, 12, 18, 24, 30, and 36) if there had been a need for contraception (i.e. if there had been any coital events) since the last visit using the following statement: *Sexual relation / activity since last visit: Yes or No*.

The study primary objective was to establish the efficacy and safety of LCS12 and LCS16 in women aged 18 to 35 years for a duration of up to 3 years.

The primary efficacy endpoint was the pregnancy rate based on the Pearl Index (PI). The cumulative failure rate (probability of getting pregnant) was also calculated using the Kaplan-Meier method as a supportive measure. Secondary efficacy variables included vaginal bleeding pattern, ovarian and cervical function, endometrial histology, and user-satisfaction questionnaire.

The sample size was based on the EMEA "Guideline on clinical investigation of steroid contraceptives in women", which requires a study large enough to have an estimate of the PI with a 2-sided 95% confidence interval (CI) such that the difference between the upper limit of the CI and the point estimate does not exceed 1. The sample size calculation assumed that the true PI was 1.0 with an annual drop out rate of 15% for the first two years and 7.5% for the third year, and a 2% loss to exposure time due to concomitant contraceptive method use.

The study design also considered requirements from the Agency conveyed at the end-of-phase 2 meeting (minutes dated 12/17/2009). The Division recommended that a minimum of 200 women should complete the full duration of the sought treatment time, that a minimum of 10,000 women cycles would be required to support the indication, and that 45% of the cycles needed to come from North American subjects.

At the pre-NDA meeting (minutes dated 08/24/2011), the Division and the Applicant agreed that this NDA would be based on pivotal phase 3 study A52238 and be supported by the phase 2 study A46796. The Division also requested the following:

- 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.
- Evaluation of efficacy will be based on the 12 month and cumulative 3-year unadjusted Pearl Indices for women aged 18-35 from the phase 3 study A52238.
- Total exposure for a subject should be expressed as the number of 28-day cycles, starting from insertion of LCS (levonorgestrel contraceptive intrauterine systems).
- 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.
- The Pearl Index should be calculated based on women aged 18-35 from the full analysis population, the total number of 28-day cycles after removing those cycles where another contraceptive method was used and including all on-treatment pregnancies. The unadjusted 12 month and unadjusted cumulative 3-year Pearl Index will be the basis for demonstrating efficacy.

3.2.2 Statistical Methodologies

The primary efficacy analysis was based on the full analysis set (FAS), which included all randomized subjects who attempted an LCS insertion at least once. Actual treatment received was used in the FAS.

The Pearl Index (PI), the primary efficacy endpoint, was calculated as x / E, where x is the number of on-treatment pregnancies and E is the relevant exposure in 100 woman-years (one woman-year is 365 days of relevant exposure). Any pregnancy between the day of insertion and seventh day after removal was counted. The 95% CI was estimated, assuming pregnancies followed a Poisson distribution, as follows:

- Lower 95% CI of PI $=0.5 \times \chi^2_{(0.025,2x)} / E$
- Upper 95% CI of PI $=0.5 \times \chi^2_{(0.975,2(x+1))} / E$

where $\chi^2_{(p,df)}$ is the p^{th} percentile from a χ^2-distribution with df degree of freedom.

The relative exposure (days or cycles) was equal to the total exposure (days or cycles) minus the following exposure time periods:

- All time periods where additional concomitant contraception or hormones were used for other reasons (data from the concomitant medication form filled out by the investigator at each visit)
- Time periods (in terms of calendar months as documented in the subject diary) of additional contraceptive method use
- The week before removal of the LCS because all subjects were instructed to use condoms for contraception starting at least 7 days prior to removal of LCS unless the removal takes place during the first days of menstruation

Relevant exposure time was calculated in either of two ways: based on days or 28-day cycles. The Applicant used days while this reviewer used 28-day cycles to calculate the PI. Based on 28-day cycles, one year of treatment is equivalent to 13 28-day cycles. The 28-day cycle PI was calculated as:

[100 × (13 28-day cycles per year) × (Number of pregnancies in time period)] / (Total number of 28-day cycles excluding cycles where back-up contraception was used)

For a missing pregnancy date, the first day of the month was imputed. If the pregnancy year was missing, the last date of treatment was imputed. For a missing expulsion or removal date or a missing last treatment date, the 15th day of the month was imputed. Missing concomitant contraceptive method use data were to be considered as no concomitant use of a contraceptive method.

As previously stated, the unadjusted PI was used by the Applicant to demonstrate efficacy. The exact rules regarding how the exposure time was calculated are presented in Table 3. For the remainder of this review, the unadjusted Pearl Index is referred to as the Pearl Index (PI).

Table 3. Study A52238: Definitions of Crude Exposure Times for the Unadjusted Pearl Indices (PI)

PI types	Reason for end of study or continuation status	Crude (total) exposure time
Unadjusted within year X PI (X=1,2,3,4,5)	Total expulsion before end of Year X	Max(Date of expulsion discovered – LCS insertion date + 1– 365(X–1), 0)
	Partial expulsion/LCS removal before end of Year X	Max(Date of LCS removal – LCS insertion date + 1– 365(X–1), 0)
	Pregnancy before end of Year X	Max(Date of conception – LCS insertion date + 1– 365(X–1), 0)
	Lost to Follow up before end of Year X	Max(Date LCS last known 'in situ'/'displace, intrauterine' – LCS insertion date + 1– 365(X–1), 0)
	Continues into X+1 year/end of Year X	365 days
Unadjusted cumulative X-year PI (X=2,3,4,5)	Total expulsion before end of Year X	Date of expulsion discovered – LCS insertion date + 1
	Partial expulsion/LCS removal before end of Year X	Date LCS removal – LCS insertion date + 1
	Pregnancy before end of Year X	Date of conception – LCS insertion date + 1
	Lost to follow up before end of Year X	Date LCS last know 'in situ'/'displace, intrauterine' – LCS insertion date + 1
	Continues into X+1 year/end of Year X	365X days
Unadjusted overall PI	Total expulsion	Date of expulsion discovered – LCS insertion date + 1
	Partial expulsion/ LCS removal	Date of LCS removal – LCS insertion date +1
	Pregnancy	Date of conception – LCS insertion date + 1
	Lost to follow up	Date LCS last known 'in situ'/'displace, intrauterine' – LCS insertion date + 1

Source: Table 1 in the Applicant's statistical analysis plan

Supportive Kaplan-Meier estimates of the cumulative pregnancy rate were also calculated using total exposure time based on days and 28-day cycles. Subjects were censored at the time of drop-out or study end. In this review, the Kaplan-Meier estimate was multiplied by 100 so it can be compared to the Pearl Index. So the probability of pregnancy is per 100 women.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

The summary of patient disposition (Table 4) was based on all randomized subjects, while the summary of demographic and baseline characteristics (Table 5) was based on the full analysis set (FAS) because efficacy was also based on the FAS.

A total of 2885 women aged 18-35 were randomized across 11 countries: U.S. (1104), Canada (184), Finland (526), France (43), Hungary (303), Netherland (170), Norway (79), Sweden (178), Argentina (137), Mexico (85), and Chile (76). As shown in Table 4, about 38% of the randomized subjects were from the U.S. and at least 200 U.S. women in each group completed 3 years of treatment, as was requested by the Division. No single study site dominated enrollment. Enrollment at each study site ranged from 1 (0.03%) subject to 97 (3.36%) subjects.

Discontinuation rates between the two treatment groups were similar. The major reason for discontinuation was adverse event (20.5%) followed by other (13.0%) and lost to follow-up (4.3%). One subject in the LCS16 treatment group did not have insertion attempted and was excluded from the FAS. Consequently, the FAS dataset had a total of 2884 subjects (1432 in LCS12 and 1452 in LCS16).

Table 4. Study A52238: Summary of Patient Disposition (All Randomized Subjects)

Disposition	Treatment		Total N=2885 (%)
	LCS12 N=1432 (%)	LCS16 N=1453 (%)	
Randomized	1432 (100.0)	1453 (100.0)	2885 (100.0)
Randomized in U.S.	540 (37.7)	564 (38.8)	1104 (38.3)
Completed first 13 Cycles	1166 (81.4)	1206 (83.0)	2372 (82.2)
Completed 3-year Study	819 (57.2)	870 (59.9)	1689 (58.5)
Completed 3-year Study (U.S. Subjects)	234 (16.3)	268 (18.4)	502 (17.4)
Discontinued/Missing:	613 (42.8)	583 (40.1)	1196 (41.5)
Withdrawal	26 (1.8)	31 (2.1)	57 (2.0)
Protocol deviation	16 (1.1)	16 (1.1)	32 (1.1)
Adverse event	313 (21.9)	278 (19.1)	591 (20.5)
Lost to follow-up	63 (4.4)	61 (4.2)	124 (4.3)
Pregnancy	9 (0.6)	10 (0.7)	19 (0.7)
Death	0 (0.0)	1 (0.1)	1 (0.0)
Other	186 (13.0)	185 (12.7)	371 (12.9)
FAS Population	1432 (100.0)	1452 (99.9)	2884 (99.97)

Source: Reviewer's analysis based on datasets EOS3, EOSM04, and EFFCYC

Patient demographic and baseline characteristics, such as age, BMI, ethnic group, and smoking history, were comparable between the two treatment groups as shown in Table 5. The mean age was 27 years, the mean BMI was 25.3, and the majority of subjects were Caucasian (at least 79%).

Table 5. Study A52238: Subject Demographic and Baseline Characteristics (FAS Population)

Variable/Parameters		Treatment		Total N=2884
		LCS12 N=1432	LCS16 N=1452	
Mean Age (SD)		27.2 (4.72)	27.1 (4.87)	27.1 (4.79)
BMI (SD)		25.3 (5.42)	25.3 (5.49)	25.3 (5.46)
Ethnic group [n (%)]:	Caucasian	1142 (79.75)	1164 (80.17)	2306 (79.96)
	Black	75 (5.24)	74 (5.10)	149 (5.17)
	Hispanic	165 (11.52)	159 (10.95)	324 (11.23)
	Asian	11 (0.77)	17 (1.17)	28 (0.97)
	Other	39 (2.72)	38 (2.62)	77 (2.67)
Current Smoker [n (%)]:	Yes	334 (23.3)	360 (24.8)	694 (24.1%)

Source: Reviewer's analysis based on Datasets DEMO01, ALC01, and SMOKE01

3.2.4 Results and Conclusions

The remainder of this review presents efficacy results for the LCS12 intrauterine system (IUS) only because the Applicant did not pursue marketing of the LCS16 IUS. This reviewer reproduced all the Applicant's results. The Applicant based their analyses on days of exposure while this reviewer based analyses on 28-day cycles of exposure. Results based on either days of exposure or cycles of exposure are similar and are presented in the tables.

Primary efficacy results:

A total of 10 pregnancies were observed in women who used LCS12 during this 3-year study (Appendix Table 9): five pregnancies in Year 1, three pregnancies in Year 2, and two pregnancies in Year 3. The Division recommendation that a minimum of 10,000 women cycles would be required to support the indication was met.

Estimates of the Pearl Index (PI) at 1 year based on either days or 28-day cycles of exposure are presented in Table 6. For the women using LCS12, the PI is 0.41 (95% CI is 0.13 to 0.96) in the first year.

Table 6. Study A52238: Pearl Index in the First Year for LCS12

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

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

Pearl Index estimates in the second and third years are all less than that for the first year (Appendix Table 10 and Table 11).

Supportive Analysis of Primary efficacy results:

Table 7 presents the cumulative pregnancy rate at the end of each time period based on both the Kaplan-Meier method and the PI definition. The cumulative pregnancy rates based on the PI definition are all less than those based on the Kaplan-Meier method at the end of the second and third years. However, the corresponding 95% CIs overlap, suggesting there are no significant differences between the two estimates. This reviewer recommends using the Kaplan-Meier estimates for cumulative pregnancy rates beyond the first year because they take into account when, over the course of the study, a pregnancy occurred.

The Kaplan-Meier cumulative pregnancy rate per 100 women in women using LCS12 is 0.39 (95% CI is 0.16 to 0.94) at the end of the first year, which is comparable to the PI presented in Table 6. The Kaplan-Meier cumulative pregnancy rate per 100 women for women using LCS12 is 0.89 (95% CI is 0.48 to 1.66) at the end of the third year.

Table 7. Study A52238: Cumulative Pregnancy Rate Based on Kaplan-Meier Estimate and PI (95% CI)

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

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

3.3 Evaluation of Safety

There was one safety analysis requested by the clinical reviewer, calculation of the Pearl Index for the rate of ectopic pregnancies by parity status based on the data from this phase 3 study A52238 and phase 2 study A46796. The clinical reviewer requested that this Pearl Index by parity status (no births or at least one birth) be presented for each study and for the combined studies at the end of the first year and at the end of the third year. The results of this analysis are presented in the Appendix **Table 16**, **Table 17**, and **Table 18**. Interpretation of these results can be found in the safety evaluation of the clinical reviewer's report.

Reviewer Comments on the Efficacy Results

Study A52238 demonstrates that LCS12 is effective in preventing pregnancy for up to 3 years in women aged 18-35. The Pearl Index is 0.41 (95% CI is 0.13 to 0.96) at the end of the first year. The corresponding Kaplan-Meier cumulative pregnancy rates per 100 women are 0.39 (95% CI is 0.16 to 0.94) at the end of the first year and 0.89 (95% CI is 0.48 to 1.66) at the third year.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Age and Geographic Region

Table 12 in the Appendix shows age subgroup analyses (≤ 25 or other). Estimates of the PI are 0.22 (95% CI is 0.01 to 1.23) for younger women and 0.53 (95% CI is 0.14 to 1.35) for older women. These results indicate that LCS12 is effective in either younger or older women.

Table 13 in the Appendix shows region subgroup analyses (U.S. subjects and non-U.S. subjects). Estimates of the PI are 0.47 (95% CI is 0.06 to 1.68) for U.S. women and 0.38 (95% CI is 0.08 to 1.12) for non-U.S. women. These results indicate that LCS12 is effective in U.S. or non-U.S. women.

An analysis by race is not performed because 80% of subjects are Caucasian.

4.2 Body Mass Index and Parity

Table 14 in the Appendix shows BMI subgroup (<30 kg/m^2 or other) analyses. Estimates of the PI are 0.40 (95% CI is 0.11 to 1.02) for smaller BMI women and 0.48 (95% CI is 0.01 to 2.69) for larger BMI women. These results indicate that LCS12 is effective in women of smaller or larger BMI.

Table 15 in the Appendix shows parity subgroup (0 births or at least one birth) analyses. Estimates of PI are 0.45 (95% CI is 0.05 to 1.62) for 0-birth women, and 0.39 (95% CI is 0.08 to 1.14) for women with at least one birth. These results indicate that LCS12 is effective in women with no births or at least one birth.

Reviewer Comments on the Subgroup Analyses

There is no evidence of a trend in lack of efficacy in the four subgroups explored: age, region, BMI, and parity.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

There were no major statistical efficacy issues encountered in this review. One minor analysis issue was that the Applicant used exposure based on days to calculate the Pearl Index while the Agency prefers exposure based on 28-day cycles. The PI results based on either days or cycles were consistently similar.

5.2 Collective Evidence

From a statistical perspective, this single phase 3 study provides evidence demonstrating the efficacy of LCS12 (13.5 mg levonorgestrel contraceptive intrauterine system) for the prevention of pregnancy for up to 3 years in women 18 to 35 years of age. The Pearl Index is 0.41 (95% CI is 0.13 to 0.96) at the end of the first year. Supportive evidence is based on the Kaplan-Meier cumulative pregnancy rate. The pregnancy rate per 100 women at the end of the first year is 0.39 (95% CI is 0.16 to 0.94) and at the end of the third year is 0.89 (95% CI is 0.48 to 1.66).

5.3 Conclusions and Recommendations

From a statistical perspective, the submitted data from study A52238 provided evidence demonstrating the efficacy of LCS12 for the prevention of pregnancy in women aged 18 to 35 years for up to 3 years.

5.4 Labeling Recommendations

The efficacy information in Table 8 is to be used for Section 14.1 of the label. (b) (4)

Table 8. Study A52238: Pearl Index at First Year and 3-Year Cumulative Contraceptive Failure Rate for LCS12

Relative Treatment Exposure Cycles[1]	Number of Pregnancies within First Year	Pearl Index (95% CI)	3-Year Cumulative Contraceptive Failure Rate Per 100 Women (95% CI)
15763	5	0.412 (0.134, 0.962)	0.89 (0.48, 1.66)

Source: Table 6 and Table 7 in this review

[1] Exposure based on 28-day cycles excluding those cycles where a back-up contraception was used

APPENDIX

Table 9. Study A52238: Pregnancies that Occurred On-Treatment and within 7 Days after Treatment for LCS12

Subject ID	Age	BMI	Date of Pregnancy (Cycle of Pregnancy)	Earliest Date of IUS Expulsion, Stop, and Study Medication	Country
120329[c]	23	22.5	07AUG10 (31)	05SEP10	Argentina
120419[a]	30	21.8	04JAN09 (9)	24FEB09	Argentina
140202[c]	27	29.0	01AUG10 (32)	03SEP10	Canada
141008[a]	26	21.9	07APR08 (2)	29APR08	Canada
160743[a]	18	19.8	01APR08 (3)	27APR08	Finland
190636[b]	23	26.2	23JUN09 (15)	24SEP09	Mexico
210519[b]	34	23.4	29OCT09 (22)	14DEC09	Norway
230303[b]	20	22.5	01MAY09 (17)	16JUN09	Sweden
245003[a]	27	21.0	03OCT08 (10)	12NOV08	United States
245932[a]	27	36.7	01JAN09 (9)	23FEB09	United States

Source: Reviewer's analysis based on dataset PREG01 and confirmed by the clinical reviewer
a: pregnancy in 1st year; b: pregnancy in 2nd year; c: pregnancy in 3rd year
Number of pregnancies in 1st year: 5 in LCS12 group

Table 10. Study A52238: Pearl Index in the Second Year for LCS12

Analysis	N	Total exposure	Back-up contraception exposure	Relevant exposure	Number of pregnancies	PI	95% CI
By Day[a]	1162	385799	15078	370721	3	0.295	(0.061, 0.863)
By Cycle[b]	1135	13687	466	13221	3	0.295	(0.061, 0.862)

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

Table 11. Study A52238: Pearl Index in the Third Year for LCS12

Analysis	N	Total exposure	Back-up contraception exposure	Relevant exposure	Number of pregnancies	PI	95% CI
By Day[a]	960	317703	16516	301187	2	0.242	(0.029, 0.876)
By Cycle[b]	938	11039	569	10470	2	0.248	(0.030, 0.897)

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

Table 12. Study A52238: Pearl Index by Age in the First Year for LCS12 (Cycle Analysis*)

Subgroup	Total cycles of exposure	Back-up contraception exposure	Relevant exposure	Number of pregnancies	PI	95% CI
age <= 25	6327	438	5889	1	0.22	(0.01, 1.23)
25 < age <= 35	10192	318	9874	4	0.53	(0.14, 1.35)

*: Reviewer's analysis based on 28-day cycles found in the analysis dataset EFFCYC
Note: PI estimates are comparable to those from Kaplan-Meier at the end of the first year. The 3-year cumulative estimates of PI by Kaplan-Meier method per 100 women are 0.97 with upper 95% CI of 2.6 for younger subgroup and 0.85 with upper 95% CI of 1.9 for older subgroup.

Table 13. Study A52238: Pearl Index by Region in the First Year for LCS12 (Cycle Analysis*)

Subgroup	Total cycles of exposure	Back-up contraception exposure	Relevant exposure	Number of pregnancies	PI	95% CI
US	5904	316	5588	2	0.47	(0.06, 1.68)
Non-US	10615	440	10175	3	0.38	(0.08, 1.12)

*: Reviewer's analysis based on 28-day cycles found in the analysis dataset EFFCYC
Note: PI estimates are comparable to those from Kaplan-Meier at the end of first year. The 3-year cumulative estimates of PI by Kaplan-Meier method per 100 women are 0.47 with upper 95% CI of 1.9 for US woman and 1.1 with upper 95% CI of 2.2 for Non-US woman.

Table 14. Study A52238: Pearl Index by BMI in the First Year for LCS12 (Cycle Analysis*)

Subgroup	Total cycles of exposure	Back-up contraception exposure	Relevant exposure	Number of pregnancies	PI	95% CI
< 30 kg/m^2	13667	605	13062	4	0.40	(0.11, 1.02)
>= 30 kg/m^2	2839	150	2689	1	0.48	(0.01, 2.69)

*: Reviewer's analysis based on 28-day cycles found in the analysis dataset EFFCYC
Note: PI estimates are comparable to those from Kaplan-Meier at the end of first year. The 3-year cumulative estimates of PI by Kaplan-Meier method per 100 women are 0.97 with upper 95% CI of 1.9 for smaller BMI subgroup and 0.47 with upper 95% CI of 3.3 for larger BMI subgroup.

Table 15. Study A52238: Pearl Index by Parity in First Year for LCS12 (Cycle Analysis*)

Subgroup	Total cycles of exposure	Back-up contraception exposure	Relevant exposure	Number of pregnancies	PI	95% CI
0 births	6304	522	5782	2	0.45	(0.05, 1.62)
1 or more births	10215	234	9981	3	0.39	(0.08, 1.14)

*: Reviewer's analysis based on 28-day cycles found in the analysis dataset EFFCYC
Note: PI estimates are comparable to those from Kaplan-Meier at the end of first year. The 3-year cumulative estimates of PI by Kaplan-Meier method per 100 women are 0.94 with upper 95% CI of 2.5 for 0 birth subgroup and 0.86 with upper 95% CI of 1.9 for at least 1 birth subgroup.

Table 16. Study A52238: Ectopic Pregnancy Rate by Parity in LCS12

Cumulative Time	Subgroup	# of Ectopic Pregnancies	Kaplan-Meier (per 100 Women)		PI Definition	
			Estimate	95% CI	PI	95% CI
1-Year	0 births	1	0.191	(0.027, 1.347)	0.225	(0.006, 1.253)
1-Year	1 birth or more	1	0.132	(0.019, 0.932)	0.130	(0.003, 0.726)
3-Year	0 births	2	0.433	(0.107, 1.735)	0.182	(0.022, 0.656)
3-Year	1 birth or more	1	0.132	(0.019, 0.932)	0.052	(0.001, 0.289)

Reviewer's analysis based on 28-day cycles found in analysis dataset EFFCYC

Table 17. Study A46796: Ectopic Pregnancy Rate by Parity in LCS12

Cumulative Time	Subgroup	# of Ectopic Pregnancies	Kaplan-Meier (per 100 Women)		PI Definition	
			Estimate	95% CI	PI	95% CI
1-Year	0 births	0	--	--	0.000	(0.000, 8.212)
1-Year	1 birth or more	0	--	--	0.000	(0.000, 2.059)
3-Year	0 births	0	--	--	0.000	(0.000, 3.457)
3-Year	1 birth or more	1	0.625	(0.088, 4.353)	0.207	(0.005, 1.154)

Reviewer's analysis based on 28-day cycles found in analysis datasets EFFCYC and parity status found in analysis dataset GYNHIS01

Table 18. Pooled Studies (A52238 + A46796): Ectopic Pregnancy Rate by Parity in LCS12

Cumulative Time	Subgroup	# of Ectopic Pregnancies	Kaplan-Meier (per 100 Women)		PI Definition	
			Estimate	95% CI	PI	95% CI
1-Year	0 births	1	0.175	(0.025, 1.239)	0.204	(0.005, 1.138)
1-Year	1 birth or more	1	0.107	(0.015, 0.754)	0.106	(0.003, 0.588)
3-Year	0 births	2	0.398	(0.099, 1.596)	0.166	(0.020, 0.598)
3-Year	1 birth or more	2	0.231	(0.058, 0.924)	0.083	(0.010, 0.300)

Reviewer's analysis based on 28-day cycles found in analysis dataset EFFCYC in both studies, and parity status found in Study A46796 analysis dataset GYNHIS01

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/s/

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12/04/2012

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12/04/2012