CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208224Orig1s000

STATISTICAL REVIEW(S)

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 #:	208224
Drug Name:	Kyleena (Levonorgestrel-releasing intrauterine system) 19.5 mg
Indication(s):	Prevention of pregnancy for up to 5 years
Applicant:	Bayer HealthCare Pharmaceuticals Inc.
Date(s):	Letter Date: November 18, 2015 PDUFA Date: September 18, 2016
Review Priority:	Standard
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Keywords:	Clinical studies, NDA review

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1 EXECUTIVE SUMMARY

Bayer HealthCare Pharmaceuticals Inc. is seeking approval of Kyleena [Levonorgestrel-releasing intrauterine system (LNG IUS, LCS16)] 19.5 mg for the prevention of pregnancy for up to 5 years. The efficacy and safety of LCS16 were assessed in a multi-center, randomized, open-label, 2-arm, parallel-group Phase 3 study (91665/310442).

There were no statistical issues identified in this submission. The pregnancy rates were estimated by the Pearl Index (PI) with its 95% confidence interval (CI) and Kaplan-Meier method. The 5 year PI was 0.29 (95% CI: 0.16, 0.50) and yearly rates were 0.16 (95% CI: 0.02, 0.58), 0.37 (95% CI: 0.10, 0.96), 0.45 (95% CI: 0.12, 1.14), and 0.15 (95% CI: 0.00, 0.85) for Year 1, 2, 3, 4, and 5, respectively. The cumulative 5-year pregnancy rate using Kaplan-Meier method was 1.4 (95% CI: 0.82 to 2.53) per 100 women.

From a statistical perspective, this study provided evidence supporting the efficacy of LCS16 for the prevention of pregnancy for up to 5 years in women 18 to 35 years of age.

2 INTRODUCTION

2.1 Overview

In this application, Bayer HealthCare Pharmaceuticals Inc. is seeking approval of LCS16 for the prevention of pregnancy for up to 5 years.

The efficacy and safety of LCS16 were assessed in one Phase 3 study (Study 91665/310442). Study 91665/310442 was a multi-center, randomized, open-label, 2-arm, parallel-group Phase 3 study. In this study both LCS12 and LCS16 were evaluated in healthy women 18-35 years of age in need of contraception. Skyla (LCS12) was approved for prevention of pregnancy up to 3 years (NDA 203159, clinical study report A52238) based on the 3-year data. In current application, Bayer is seeking approval of LCS16 in prevention of pregnancy for up to 5 years. Table 1 presents a brief summary of the study.

Table 1: Brief summary of the pivotal study

Study Number (Country/#Sites) Date First Subject Enrolled, Date last Subject Completed	Subject Population	Treatment	Full Analysis Set (FAS)
91665/310442 (US/56, CA/13, FI/15, FR/8, HU/8, NL/9, NO/5, SE/12, AR/5, MX/4, CL/3) August 20, 2007, June 07 2013	Women between 18 and 35 years of age, with regular menstrual cycles (length of cycle 21-35 days), in good general health, and in need of contraception	LNG IUS 19.5mg	1452

Source: Statistical Reviewer's listing.
Full Analysis Set: all subjects who were randomized to LCS16 and received treatment (had at least one insertion attempt).

2.2 Data Sources

The application was submitted electronically. The submitted SAS datasets were completed. The review items are located in the CDER Electronic Document Room as described below:

- The completed study report is located at \\CDSESUB1\evsprod\NDA208224\0000\m5\53-clin-stud-rep\535-rep-effic-safety-

stud\prevention-of-pregnancy\5352-stud-rep-uncontr\91665-ph37274 under submission dated November 18, 2015 (eCTD Sequence Number 0000)

- Raw and derived datasets used for analysis and the datasets define files are located at \\CDSESUB1\evsprod\NDA208224\0000\m5\datasets\91665-ph37274\tabulations\sdtm and \\CDSESUB1\evsprod\NDA208224\0000\m5\datasets\91665-ph37274\analysis\legacy\datasets under submission dated November 18, 2015 (eCTD Sequence Number 0000)
- SAS program to generate key efficacy analysis datasets and results in the clinical study report is located at \\CDSESUB1\evsprod\NDA208224\0000\m5\datasets\91665-ph37274\analysis\legacy\programs under submission dated November 18, 2015 (eCTD Sequence Number 0000).

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The submitted datasets and definition files are accessible. This reviewer was able to reproduce the primary efficacy results as presented in the study report from the derived efficacy dataset.

3.2 Evaluation of Efficacy

The Applicant has submitted one pivotal clinical study 91665/310442 to demonstrate the efficacy and safety of LCS16 for the prevention of pregnancy for up to 5 years.

3.2.1 Study Design and Endpoints

Study 91665/310442 was a multi-center, randomized, open-label, 2-arm, parallel-group Phase 3 study. In this study both LCS12 and LCS16 were evaluated in healthy women 18-35 years of age in need of contraception. Skyla (LCS12) was approved for prevention of pregnancy up to 3 years (NDA 203159, clinical study report A52238) based on the 3-year data. In current application, Bayer is seeking approval of LCS16 in prevention of pregnancy for up to 5 years.

A total of 2820 generally healthy women 18 to 35 years of age desiring contraception were to be randomized to 2 equal-sized treatment arms (1410 subjects per dose). The study population in the extension phase consisted of subjects who had already been using LCS16 for contraception in the first part of the study (for 3 years), and who wished to continue with the method in the extension phase of the study (for up to 2 additional years). The continuation of the study for each subject was to be documented at Visit 10 (36 months). Those subjects, who entered the LCS16 extension phase were to have 4 additional scheduled study visits: Visits 11 (Month 42), 12 (Month 48), 13 (Month 54), and 14 (Month 60). The Visit 14 was to be performed at the end of the study. The maximum duration of treatment was to be 5 years.

The objective of the study was to assess the safety, efficacy, and pharmacokinetics of LCS16, a new intrauterine contraceptive system for up to 5 years of use.

The pregnancy rates were estimated by Pear Index (PI) and the Kaplan-Meier method.

3.2.2 Statistical Methodologies

Full analysis set (FAS) included all subjects randomized and who received treatment (had at least one insertion attempt). Both efficacy and safety analyses were based on FAS. The primary

efficacy variable was the occurrence of pregnancy. The Pear Index is defined as the number of pregnancies per 100 woman-years, calculated using the model specified below. In addition, the corresponding 2-sided 95% confidence interval was calculated.

Mathematical model of the calculation of the Pearl Index assumed that the number of pregnancies follows a Poisson distribution, and the point estimate and the corresponding 95 % CI can be calculated as follows:

PI = x/E,
Lower 95 % confidence limit of PI = 0.5 x χ^2 (0.025, 2x) /E
Upper 95 % confidence limit of PI = 0.5 x χ^2 (0.975, 2(x+1)) /E
Where x = number of pregnancies,
E = exposure in 100 woman-years (one woman-year is 365 days of treatment exposure),
χ^2 (alpha, df) is the alpha quantile from 2-distribution with df degrees of freedom.

Additionally, Pearl Index was also reported by parity, age group, body mass index (BMI), and for ectopic pregnancies.

Sponsor presented both unadjusted and adjusted Pearl Indices, but per agreement between the Division and the Applicant, the review focused on the unadjusted PI only. The definition of unadjusted PI is presented in Table 2.

Table 2: Definition of crude exposure times for the unadjusted Pearl Index - Study 91665/310442

PI	Reason for end of study/continuation status	Crude exposure time [days]
x^{th} year PI (x=1,2,3,4,5)	Total expulsion in year x	Max (Date, when expulsion was discovered – LCS insertion date+1-365*(x-1), 0)
	Partial Expulsion/ LCS removal in year x	Max (Date of LCS removal - LCS insertion date +1-365*(x-1),0)
	Pregnancy in year x	Max(Date of conception - LCS insertion date +1-365*(x-1),0)
	Lost to Follow up during year x	Max (Date LCS last known 'in situ' or 'displaced, intrauterine' - LCS insertion date +1-365*(x-1),0)
	Continues into x^{th} year of treatment	365 days
x-year PI (x=2,3,4,5)	Total expulsion before end of year x	Date, when expulsion was 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 known 'in situ' or 'displaced, intrauterine' - LCS insertion date +1
	Continues into $(x+1)^{th}$ year of treatment	365*x days
Overall PI	Total expulsion	Date, when expulsion was 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' or 'displaced, intrauterine' - LCS insertion date +1

Source: Table 1 in the Study Statistical Analysis Plan.

As a secondary analysis, the cumulative failure rate, i.e. the probability of getting pregnant, was also calculated using the Kaplan-Meier method, where subjects who were not pregnant were censored at the date of dropout or end of study.

Exposure times to be subtracted:

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 were excluded from the exposure time, but pregnancies in these intervals were counted for the PI calculation.

Sample Size Calculation

Applicant claimed that they followed the European Medicines Agency (EMA) Guideline on clinical investigation of steroid contraceptives in women (EMA/CPMP/EWP/519/ Rev1, July 2005) to determine the study sample size. Applicant's rationale to calculate the sample size is listed in this section.

EMA Guidance requires the performance of a study large enough to give the PI with a 2-sided 95% CI such that the difference between the upper limit of the CI and the point estimate (as pregnancies per 100 woman-years) does not exceed 1. The sample size for the study was chosen to be large enough to fulfill this requirement also for the third year alone in each of the two treatment groups. The assumptions were as follows:

- The true PI is 1.0,
- The annual dropout rate is 15%,
- Due to the use of an additional concomitant contraceptive method, the exposure time to be reduced by an additional 2%.

For a true PI of 1, the relevant exposure time should be 923 woman-years. Therefore, under the assumptions stated above, 923 / (0.85*0.85*0.925*0.98) = 1410 subjects were adequate with sufficient exposure time in the third year of treatment. This sample size was also adequate for a true PI of 0.8, assuming the same drop-out rate and loss of exposure time due to additional concomitant contraceptive method of 11% (839 (=exposure time needed) / 0.85*0.85*0.925*0.89)=1410).

The number of women who were to complete 5 years of LCS16 treatment was expected to be approximately 237 [237≈(2885/2)*(0.8^5)*0.5, where 2885 was the total number of randomized women]. This sample size was considered adequate for the extension phase assuming 20% yearly dropout rate and 50% of the women completing the 3 years of LCS16 treatment would continue the treatment in the extension phase. This met the EMA guideline requirement that for long-acting products the number of women completing the claimed duration of use should be at least 200.

3.2.3 Subject Disposition, Demographics and Baseline Characteristics

A total of 3661 subjects from 11 countries in 138 study sites were screened for the study. 1453 subjects were randomized to LCS16. One subject (Subject ID: 245532) was randomized but no insertion with LCS16 was attempted and was not included in the analysis population (FAS).

Table 3 summarizes subject disposition of LCS16 for the first 3 years and extension phase (up to 5 years). Overall, 38.8% subjects were from the US sites. 49.1% subjects completed the study phase (3 years or extension phase). The most common reasons for study discontinuation were adverse event (21.6%), other reasons (19.6%), lost to follow-up (5.0%), and withdrawal of consent (5.6%).

There were 6 subjects who actually received treatments that were different from the planned treatments. The planned treatment was the treatments a subject was randomized to. Applicant used the planned treatment for the analysis. The 6 subjects (planned treatment) were 120314 (LCS16), 200232 (LCS16), 230708 (LCS16), 240721 (LCS12), 244704 (LCS16), 245708 (LCS12).

Table 3: Subject Disposition – Study 91665/310442

Disposition	LCS 16 first 3 years N=1453 n (%)	LCS16 extension (after 3 years) N=707 n (%)	LCS16 Overall N=1453 n (%)
Screened	3661		3661
Randomized	1453 (100%)		
Randomized in US site	563 (38.8%)	198 (28.0%)	563 (38.8%)
Study medication administered	1452 (>99.9%)	707 (100%)	1452 (>99.9%)
Continued to the extension phase	707 (48.7%)		
Not continued to the extension phase	745 (51.3%)		
Completed study phase (3 years or extension)	163 (11.2%)	550 (77.8%)	713 (49.1%)
Prematurely discontinued	583 (40.1%)	157 (22.2%)	740* (50.8%)
Reason for discontinuation			
Withdrawal of consent	31 (2.1%)	3 (0.4%)	34 (2.3%)
Protocol deviation	16 (1.1%)	2 (0.3%)	18 (1.2%)
Adverse event	278 (19.1%)	36 (5.1%)	314 (21.6%)
Death	1 (<0.1%)	1 (0.1%)	2 (0.1%)
Lost to Follow-up	61 (4.2%)	12 (1.7%)	73 (5.0%)
Pregnancy	10 (0.7%)	3 (0.4%)	13 (0.9%)
Other	186 (12.8%)	100 (14.1%)	286* (19.6%)

Source: Reviewer's analysis and Table 8-2 in the Study 91665/310442 clinical study report.

* Subject 245532 was randomized but no insertion was attempted. She was not included in the FAS. Subject 150147 had failure insertion. She was included in the FAS. Both were counted as "prematurely discontinued" study and reason for discontinuation of "Other."

Demographics and baseline characteristics based on FAS were summarized in Table 4. Subject mean age was 27.1 years old (range 18 to 35). The majority of subjects were Caucasian (80.2%), followed by Hispanic (11.0%). The mean BMI was 25.3 kg/m^2 (range 15.2 to 57.6). The average menstrual cycle length reported at screening was 28.3 days. The primary contraceptive method at screening was condom (40.3%) and oral contraceptive (34.0%). 63.4% subjects had normal average intensity of bleeding.

Table 4. Demographics and Baseline Characteristics – Study 91665/310442 (FAS)

Characteristics	Non-extension group N=745 n (%)	Extension Group N=707 n (%)	Overall N = 1452 n (%)
Variable category			
≤ 25 years	310 (41.6%)	254 (35.9%)	564 (38.8%)
> 25 years ≤ 35 years	435 (58.4%)	453 (64.1%)	888 (61.2%)
Age (years)			
Mean (SD)	26.6 (4.7)	27.6 (5.0)	27.1 (4.9)
Max	18, 35	18, 35	18, 35
Race			
Caucasian	581 (78.0%)	583 (82.5%)	1164 (80.2%)
Black	55 (7.4%)	19 (2.7%)	74 (5.1%)
Hispanic	81 (10.9%)	78 (11.0%)	159 (11.0%)
Asian	9 (1.2%)	8 (1.1%)	17 (1.2%)
Other	19 (2.6%)	19 (2.7%)	38 (2.6%)
Weight (kg)			
Mean (SD)	69.7 (16.2)	67.6 (14.6)	68.7 (15.5)
Min, Max	39, 173	38, 153	38, 173
Height (cm)			
Mean (SD)	165.1 (7.0)	164.2 (7.2)	164.7 (7.1)
Min, Max	142, 186	124, 188	124, 188
Body mass index (kg/m^2)			
Mean (SD)	25.54 (5.66)	25.09 (5.30)	25.32 (5.49)
Min, Max	15.2, 56.5	15.2, 57.6	15.2, 57.6
Currently sexually active			
No	12 (1.6%)	5 (0.7%)	17 (1.2%)
Yes	733 (98.4%)	702 (99.3%)	1435 (98.8%)
Current smokers			
No	555 (74.5%)	537 (76.0%)	1092 (75.2%)
Yes	190 (25.5%)	170 (24.0%)	360 (24.8%)
Number of cigarettes per day			
Mean (SD)	7.8 (5.8)	8.0 (6.2)	7.9 (5.9)
Min, Max	0, 25	0, 20	0, 25
Previous births			
0	312 (41.9%)	262 (37.1%)	574 (39.5%)
>0	433 (58.1%)	445 (62.9%)	878 (60.5%)
Cycle average length			
Mean (SD)	28.2 (2.3)	28.5 (2.0)	28.3 (2.2)
Min, Max	0, 35	21, 36	0, 36
Previous Contraceptive			
Condom	324 (43.5%)	261 (36.9%)	585 (40.3%)
Oral Contraceptive	238 (31.9%)	255 (36.1%)	493 (34.0%)
Average Intensity of bleeding			
None	2 (0.3%)	1 (0.1%)	3 (0.2%)
Spotting	1 (0.1%)	4 (0.6%)	5 (0.3%)
Light	83 (11.1%)	104 (14.7%)	187 (12.9%)
Normal	472 (63.4%)	453 (64.1%)	925 (63.7%)
Heavy	187 (25.1%)	145 (20.5%)	332 (22.9%)

Key: BMI = body mass index; SD = standard deviation. Note: Percentages were based on N.
Source: Tables 8-7, 8-8, 8-12, 8-13 in the clinical study report and reviewer's analysis.

3.2.4 Results and Conclusion

A total of 13 pregnancies were observed during the 5-year study. Numbers of pregnancies in each of the 5 years were 2, 4, 4, 1, and 2, respectively. One additional pregnancy (from Subject 245406) occurred 20 days after IUS was removed and was not accounted towards the efficacy endpoint. List of pregnancies are shown in Table 13 in the Appendix. The overall unadjusted PI was 0.29 (95% CI: 0.16, 0.50, Table 5). The unadjusted PIs for each of the 5 years were 0.16 (95% CI: 0.02, 0.58), 0.37 (95% CI: 0.10, 0.96), 0.45 (95% CI: 0.12, 1.14), 0.15 (95% CI: 0.00, 0.85), and 0.36 (95% CI: 0.04, 1.29), respectively.

Note that there were 773 subjects at the beginning of Year 4, which was more than the number of subjects enrolled in the extension phase of the study, the reason being that some subjects in the 3-year study had treatment exposure longer than 3-years and they were considered at risk for pregnancy at the beginning of Year 4.

Table 5: Unadjusted PI based on woman-years (WY) – Study 91665/310442 (FAS)

Time	Subjects N	Pregnancies n	Relevant exposure WY	Pearl Index	95% CI
Overall	1452	13	4437.31	0.29	0.16, 0.50
Year 1	1452	2	1252.43	0.16	0.02, 0.58
Year 2	1206	4	1066.87	0.37	0.10, 0.96
Year 3	1010	4	897.75	0.45	0.12, 1.14
Year 4	773	1	659.17	0.15	0.00, 0.85
Year 5	636	2	558.30	0.36	0.04, 1.29
2 years	1452	6	2319.30	0.26	0.09, 0.56
3 years	1452	10	3217.05	0.31	0.15, 0.57
4 years	1452	11	3876.22	0.28	0.14, 0.51
5 years	1452	13	4434.53	0.29	0.16, 0.50

Source: Table 9-1 in the clinical study report. 1WY=365 days of treatment exposure.

Eight of the 13 pregnancies were ectopic pregnancies. The unadjusted PIs for subgroup analysis are presented in Table 11 and Table 12 in the Appendix. Overall, 5-year PI for ectopic pregnancies was 0.18 (95% CI: 0.08, 0.36). The PI for ectopic pregnancies was similar in the 18-25 and >25-35 years age groups, and numerically higher in the nulliparous women group, women with BMI greater than or equal to 30 kg/m^2, and in US sites.

Applicant also calculated the Pearl Index based on 28-day cycles of exposure (presented in Table 6). There were 57,335 28-day cycles in the study and 57, 313 cycles over 5 years of treatment exposure. For the women using LCS16, the overall PI was 0.29 (95% CI was 0.16, 0.50). The result was consistent with the PI based on woman-years.

Note that there were 1414 subjects overall in Table 6. That was because 38 subjects in the study had actual treatment exposure less than 28 days and were not counted as a cycle for the PI calculation.

Table 6: Unadjusted PI based on 28-day cycle – Study 91665/310442 (FAS)

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

Source: Table 1.2/27 in the Integrated Summary of Efficacy.

The cumulative pregnancy rates using Kaplan-Meier method is presented in Table 7. The probability of getting pregnant over 5 years use of LCS16 was 1.4 per 100 women (95% CI: 0.82, 2.53).

Table 7: Cumulative pregnancy rate – Study 91665/310442 (FAS)

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

Source: Table 9-3 in the clinical study report.

3.3 Other Special/Subgroup Populations

The unadjusted PI by subgroups of age, parity, BMI, and region is presented in Table 8. The Pearl Index was numerically higher in >25-35 years age group, parous women, women with BMI greater than or equal to 30 kg/m^2, and at US sites.

Table 8: Cumulative 5-year analysis of unadjusted PI by subgroups – Study 91665/310442 (FAS)

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

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

There were compliance concerns from Dr. Ronald Ackerman's site (Site 2415) and Dr. Richard Muckerman's site (Site 2434). A sensitivity analysis was conducted to assess the impact on the efficacy results if the 19 subjects from Site 2415 and 4 subjects from Site 2434 were excluded from FAS. The results are shown in Table 9 and Table 10. The 5 year PI was 0.30 (95% CI: 0.16, 0.51) and cumulative 5-year pregnancy rate was 1.5 per 100 women. The results did not differ markedly with or without subjects from these two sites.

Table 9: Unadjusted PI based on woman-years (WY) excluding subjects from Sites 2415 and 2434 – Study 91665/310442 (FAS)

Time	Subjects N	Pregnancies n	Relevant exposure WY	Pearl Index	95% CI
Overall	1429	13	4393.96	0.30	0.16, 0.51
Year 1	1429	2	1234.02	0.16	0.02, 0.59
Year 2	1187	4	1052.42	0.38	0.10, 0.97
Year 3	997	4	887.33	0.45	0.12, 1.15
Year 4	769	1	659.10	0.15	0.00, 0.85
Year 5	636	2	558.30	0.36	0.04, 1.29
2 years	1429	6	2286.44	0.26	0.10, 0.57
3 years	1429	10	3173.77	0.32	0.15, 0.58
4 years	1429	11	3832.87	0.29	0.14, 0.51
5 years	1429	13	4391.18	0.30	0.16, 0.51

Source: Reviewer's analysis.

Table 10: Cumulative pregnancy rate excluding subjects from Sites 2415 and 2434 – Study 91665/310442 (FAS)

Time	Subjects N	Pregnancies n	Relevant exposure WY	Cumulative pregnancy rate(%)	95% CI
Year 1	1452	2	4393.96	0.180	0.045, 0.717
Year 2	1206	4	1234.02	0.376	0.141, 1.00
Year 3	1010	4	1052.42	0.428	0.161, 1.136
Year 4	773	1	887.33	0.147	0.021, 1.038
Year 5	636	2	659.10	0.333	0.083, 1.324
2 years	1452	6	558.30	0.547	0.246, 1.217
3 years	1452	10	2286.44	0.969	0.521, 1.801
4 years	1452	11	3173.77	1.111	0.612, 2.024
5 years	1452	13	3832.87	1.457	0.831, 2.549

Source: Reviewer's analysis.

3.4 Safety analysis

Safety information can be found in the clinical reviewer's report.

4 SUMMARY AND CONCLUSIONS

4.1 Statistical Issues

There were no statistical issues identified in this submission.

4.2 Collective Evidence

The efficacy of LCS16 was demonstrated as shown by the estimated Pearl Index (PI) and Kaplan-Meier method. The 5 year PI and its 95% CI was 0.29 (95% CI: 0.16, 0.50) and the cumulative 5-year pregnancy rate by Kaplan-Meier method was 1.4 (95% CI: 0.82 to 2.53) per 100 women. The yearly PIs over 5 years were 0.16 (95% CI: 0.02, 0.58), 0.37 (95% CI: 0.10, 0.96), 0.45 (95% CI: 0.12, 1.14), and 0.15 (95% CI: 0.00, 0.85) at Year 1, Year 2, Year 3, Year 4, and Year 5, respectively.

4.3 Conclusions and Recommendations

From a statistical perspective, study provided evidence supporting the efficacy of LCS16 for the prevention of pregnancy for up to 5 years in women 18 to 35 years of age.

5 Appendix

Table 11: Unadjusted PI for ectopic pregnancies - Study 91665/310442 (FAS)

Time	Subjects N	Pregnancies n	Relevant exposure WY	Pearl Index	95% CI
Overall	1452	8	4437.31	0.18	0.08, 0.36
Year 1	1452	2	1252.43	0.16	0.02, 0.58
Year 2	1206	3	1066.87	0.28	0.06, 0.82
Year 3	1010	2	897.75	0.22	0.03, 0.80
Year 4	773	1	659.17	0.15	0.00, 0.85
Year 5	636	0	558.30	0.00	0.00, 0.66
2 years	1452	5	2319.30	0.22	0.07, 0.50
3 years	1452	7	3217.05	0.22	0.09, 0.45
4 years	1452	8	3876.22	0.21	0.09, 0.41
5 years	1452	8	4434.53	0.18	0.08, 0.36

Source: Table 14.2.1/9 in the clinical study report.

Table 12: 5 year unadjusted PI for ectopic pregnancies by subgroups – Study 91665/310442 (FAS)

Category	Subjects N	Pregnancies n	Relevant exposure WY	Pearl Index	95% CI
Age					
18-25 years	564	3	1628.76	0.18	0.04, 0.54
>25-35 years	888	5	2808.55	0.18	0.06, 0.42
Parity					
Nulliparous	574	4	1636.80	0.24	0.07, 0.63
Parous	878	4	2800.51	0.14	0.04, 0.37
BMI					
<30 kg/m^2	1198	6	3703.97	0.16	0.06, 0.35
≥30kg/m^2	250	2	721.27	0.28	0.03, 1.00
Region					
US	563	4	1446.95	0.28	0.08, 0.71
Non-US	889	4	2990.36	0.13	0.04, 0.34

Source: Table 14.2.1/10, 11, 12 in the clinical study report and reviewer's analysis.

Table 13: Listing of pregnancies

Subject ID	Country	Continued in extension?	Pregnant year	Age/BMI/Parity	Pregnancy implantation	Insertion date/Removal date/IUS last compliant	Conception date/Conception date (imputed)
160423	FI	No	1	26/35/1 birth or more	Ectopic	18DEC2007/09OCT2008/09OCT2008	26SEP2008/26SEP2008
160927	FI	No	3	33/19 9/1 birth or more	Other	22OCT2007/10FEB2010/10FEB2010	10DEC2009/10DEC2009
180112	HU	No	2	33/33 8/1 birth or more		04DEC2007/ 04JUN2009/29DEC2008	02MAY2009/02MAY2009
180317	HU	No	2	33/31 5/1 birth or more	Ectopic	22NOV2007/03JAN2009/03JAN2009	07DEC2008/07DEC2008
200609	NL	No	2	32/19 9/1 birth or more	Ectopic	03/JAN2008/21DEC2009/21DEC2009	NKOCT2009/01OCT2009
242321	US	No	2	31/21 1/0 births	Ectopic	21APR2008/19JUL2010/19JUL2010	NKNK2010/01JAN2010
243228	US	No	1	23/27 61birth or more	Ectopic	20MAY2008/06MAY2009/06MAY2009	28MAR2009/28MAR2009
243703	US	No	3	26/42 9/1 birth or more		13DEC2007/ /10FEB2010	08FEB2010/08FEB2010
243932	US	No	3	29/21 3/0 births	Ectopic	21FEB2008/08MAR2011/08MAR2011	NKFEB2011/01FEB2011
244519	US	No	3	25/26 9/0 births	Ectopic	10APRI2008/ 18JUN2010/14APR2010	08JUN2010/08JUN2010
245406	US	No	1 (20 days after IUS removal)	26/27 2/1 birth or more		27FEB2008/ /05SEP2008	08OCT2008/08OCT2008
120324	AR	Yes	5	32/25/2/1 birth or more		01MAY2008/21SEP2012/21MAY2012	06AUG2012/06AUG2012
170411	FR	Yes	4	23/26 3/0 birth	Ectopic	03JAN2008/07JUN2011/14JAN2011	17MAY2011/17MAY2011
180616	HU	Yes	5	33/18 7/1 birth or more	Other	22NOV2007/09MAR2012/08MAR2012	16FEB2012/16FEB2012

Source: Table 14 2 1/17 in the clinical study report

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/s/

WEIYA ZHANG
08/19/2016

MAHBOOB SOBHAN
08/19/2016

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 208224

Applicant: Bayer Healthcare Pharmaceuticals Inc.

Stamp Date: 18NOV2015

Drug Name: Levonorgestrel-releasing intrauterine system (LNG IUS) containing 19.5 mg LNG (LCS16)

NDA/BLA Type: NDA

Proposed Indication for Use: Prevention of pregnancy for up to 5 years

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	x			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	x			* Upon agreement in the pre-NDA communication, Applicant provided the narrative portions of the ISE and ISS by cross-reference to the corresponding Module 2 summaries (2.7.3 and 2.7.4, respectively) and to include the tables, appendices, and datasets in Module 5.3.5.3.
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	x			Efficacy analysis by parity, age-group and BMI were investigated in study PH-37274 (protocol 91665/310442). (b) (4)
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	x			The datasets for ISS, ISE, study PH-37274 (protocol 91665/310442) are available under this NDA. Datasets for study CSR A46796 (protocol 308901) were submitted in NDA203159 and not resubmitted in current NDA.

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? ____Yes____

If the NDA/BLA is not fileable from the statistical perspective, state the reasons and provide comments to be sent to the Applicant.

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

1. It was mentioned in the Pre-NDA Meeting Information Package page 44 that "… the post-study Pregnancy Forms from the +7-day pregnancies are not part of the study report, they would be provided in a separate subfolder under the study report folder in Module 5.3.5.2. " It appears that CRF pages are presented in CRF folder in Module 5.3.5.2 (\NDA208224\0000\m5\53-clin-stud-

rep\535-rep-effic-safety-stud\prevention-of-pregnancy\5352-stud-rep-uncontr\91665-ph37274\crf). Clarify:

a. Which subjects had post-study pregnancies and its post-study Pregnancy Forms location in the NDA package.
b. The location and the names of the raw and analysis datasets for the post-study pregnancy information.

2. It was mentioned in the Pre-NDA Meeting Information Package page 44 that "… there were 2 pregnancies that were reported after the subjects completed the phase 3 clinical stud in the LCS16 group…these pregnancies will not be included in the PI+7 day calculations. Available information on these pregnancies will be included in the NDA." Identify the subject IDs for these 2 pregnancies. Provide the location of available information (CRF, post-study Pregnancies Forms, etc.). If these pregnancies were included in the datasets, please clarify the datasets name and location.

3. Applicant mentioned in the NDA208224 Module 1.2 Reviewer's Guide Section 3.5 that "… Bayer became aware of statistical programming finding that led to the recent amendment of all Phase 3 Clinical Study Reports with LCS16 and/or LCS12 submitted in this application (Module 5.3.5)… All data presented in this submission are current and reflect the results in the amended reports." Submit the SAS program BLDWHO.sas used to generate the BLDWHO dataset mentioned in the 310442_programming_specs_d_bldwho_v10.doc for study CSR PH-37274 (protocol 91665/310442).

Content Parameter (possible review concerns for 74-day letter)	**Yes**	**No**	**NA**	**Comment**
Designs utilized are appropriate for the indications requested.	x			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	x			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			x	No Interim analyses or DSMB were specified in the protocol.
Appropriate references for novel statistical methodology (if present) are included.			x	No novel statistical methodologies were implemented in the studies.
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	x			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	x			

Weiya Zhang, Ph.D. 1/14/2016

Reviewing Statistician Date

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Mahboob Sobhan, Ph.D.	1/14/2016
Supervisor/Team Leader	Date

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/s/

WEIYA ZHANG
01/14/2016

MAHBOOB SOBHAN
01/14/2016