CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208224Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW ADDENDUM

NDA:	208224
Submission Type:	505(b)(1)
Brand Name:	Kyleena®
Generic Name:	Levonorgestrel-releasing intrauterine system
Submission Dates:	11/18/2015, 06/18/2016
PDUFA Goal Date:	September 16, 2016
Priority:	Standard
Proposed Indication:	Prevention of pregnancy for up to 5 years
Formulation and Dosing Regimen:	Intrauterine system containing 19.5 mg of levonorgestrel with an initial release rate of 17.5 µg/day
Applicant:	Bayer HealthCare Pharmaceuticals Inc.
Reviewer:	Lin Zhou, Ph.D.
Team Leader:	Myong Jin Kim, Pharm.D.
OCP Division	DCP III
OND Division	OND/ODEIII/DBRUP

1. Executive Summary

When the clinical pharmacology review of NDA 208224 was signed off in DARRTS on 08/19/2016, the applicant and the division had not reached agreement regarding the language in the package insert labeling of Kyleena®. The final agreement was reached on 09/15/2016 and there are no pending issues from the Office of Clinical Pharmacology. The highlights of the prescribing information and Clinical Pharmacology relevant sections of the final agreed upon package insert labeling are included in Section 2 of this addendum.

1.1 Recommendation

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

2. Final Agreed Upon Package Insert Labeling

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use KYLEENA safely and effectively. See full prescribing information for KYLEENA.

KYLEENA (levonorgestrel-releasing intrauterine system)
Initial U.S. Approval: 2000

INDICATIONS AND USAGE

Kyleena is a progestin-containing intrauterine system (IUS) indicated for prevention of pregnancy for up to 5 years. (1)

DOSAGE AND ADMINISTRATION

- Release rate of levonorgestrel (LNG) is 17.5 mcg/day after 24 days and declines to 7.4 mcg/day after 5 years; Kyleena must be removed or replaced after 5 years. (2)
- To be inserted by a trained healthcare provider using strict aseptic technique. Follow insertion instructions exactly as described. (2)
- Patient should be re-examined and evaluated 4 to 6 weeks after insertion; then yearly or more often if clinically indicated. (2.2)

DOSAGE FORMS AND STRENGTHS

- One sterile intrauterine system consisting of a T-shaped polyethylene frame with a steroid reservoir containing 19.5 mg levonorgestrel, packaged within a sterile inserter (3)

CONTRAINDICATIONS

- Pregnancy or suspicion of pregnancy. Cannot be used for post-coital contraception (emergency contraception) (4)
- Congenital or acquired uterine anomaly if it distorts the uterine cavity (4)
- Acute pelvic inflammatory disease (PID) or a history of PID unless there has been a subsequent intrauterine pregnancy (4)
- Postpartum endometritis or infected abortion in the past 3 months (4)
- Known or suspected uterine or cervical neoplasia (4)
- Known or suspected breast cancer or other progestin-sensitive cancer (4)
- Uterine bleeding of unknown etiology (4)
- Untreated acute cervicitis or vaginitis or other lower genital tract infections (4)
- Acute liver disease or liver tumor (benign or malignant) (4)
- Increased susceptibility to pelvic infection (4)
- A previous intrauterine device (IUD) that has not been removed (4)

1 INDICATIONS AND USAGE

Kyleena is indicated to prevent pregnancy for up to 5 years. Replace the system after 5 years if continued use is desired.

2 DOSAGE AND ADMINISTRATION

Kyleena contains 19.5 mg of levonorgestrel (LNG) released *in vivo* at a rate of approximately 17.5 mcg/day after 24 days. This rate decreases progressively to 9.8 mcg/day after 1 year and to 7.4 mcg/day after 5 years. The average *in vivo* release rate of LNG is approximately 9 mcg/day over a period of 5 years. *[See Clinical Pharmacology (12.3).]*

7 DRUG INTERACTIONS

No drug-drug interaction studies have been conducted with Kyleena.

Drugs or herbal products that induce or inhibit LNG metabolizing enzymes, including CYP3A4, may decrease or increase, respectively, the serum concentrations of LNG during the use of Kyleena. However, the contraceptive effect of Kyleena is mediated via the direct release of LNG into the uterine cavity and is unlikely to be affected by drug interactions via enzyme induction or inhibition.

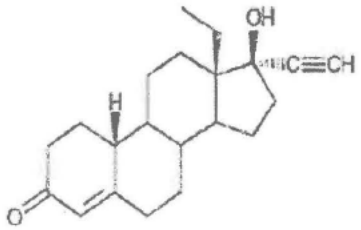
8.4 Pediatric Use

[redacted](b) (4) Efficacy is expected to be the same for postpubertal females under the age of 18 as for users 18 years and older. Use of this product before menarche is not indicated.

11 DESCRIPTION

Kyleena (levonorgestrel-releasing intrauterine system) contains 19.5 mg of LNG, a progestin, and is intended to provide an initial release rate of approximately 17.5 mcg/day of LNG after 24 days.

Levonorgestrel USP, (-)-13-Ethyl-17-hydroxy-18,19-dinor-17α-pregn-4-en-20-yn-3-one, the active ingredient in Kyleena, has a molecular weight of 312.4, a molecular formula of $C_{21}H_{28}O_2$, and the following structural formula:



11.1 Kyleena

Kyleena consists of a T-shaped polyethylene frame (T-body) with a steroid reservoir (hormone elastomer core) around the vertical stem. The white T-body has a loop at one end of the vertical stem and two horizontal arms at the other end. The reservoir consists of a whitish or pale yellow cylinder, made of a mixture of LNG and silicone (polydimethylsiloxane), containing a total of 19.5 mg LNG. The reservoir is covered by a semi-opaque silicone membrane, composed of polydimethylsiloxane and colloidal silica. A ring composed of 99.95% pure silver is located at the top of the vertical stem close to the horizontal arms and is visible by ultrasound. The polyethylene of the T-body is compounded with barium sulfate, which makes it radiopaque. A monofilament blue polypropylene removal thread is attached to a loop at the end of the vertical stem of the T-body. The polypropylene of the removal thread contains <0.5% phthalocyaninato(2-) copper as a colorant (see Figure 10).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The local mechanism by which continuously released LNG contributes to the contraceptive effectiveness of Kyleena has not been conclusively demonstrated. Studies of Kyleena and similar LNG IUS prototypes have suggested several mechanisms that prevent pregnancy: thickening of cervical mucus preventing passage of sperm into the uterus, inhibition of sperm capacitation or survival, and alteration of the endometrium.

12.2 Pharmacodynamics

Kyleena has mainly local progestogenic effects in the uterine cavity. The local concentrations of LNG lead to morphological changes including stromal pseudodecidualization, glandular atrophy, a leukocytic infiltration and a decrease in glandular and stromal mitoses.

In clinical trials with Kyleena, ovulation was assessed based on serum progesterone values >2.5 ng/mL in one study and serum progesterone values >2.5 ng/mL together with serum estradiol levels <27.24 pg/mL in another study. Evidence of ovulation by these criteria was seen in 23 out of 26 women in the first year, in 19 out of 20 women in the second year, and in all 16 women in the third year. In the fourth year, evidence of ovulation was observed in the one woman remaining in the subset and in the fifth year, no women remained in this subset.

12.3 Pharmacokinetics

Absorption

Low doses of LNG are administered into the uterine cavity with the Kyleena intrauterine delivery system. The *in vivo* release rate is approximately 17.5 mcg/day after 24 days and is reduced to approximately 15.3 mcg/day after 60 days and to 9.8 mcg/day after 1 year. It then declines progressively to approximately 7.9 mcg/day after 3 years and 7.4 mcg/day after 5 years. The average LNG *in vivo* release rate is approximately 9 mcg/day over the period of 5 years.

In a subset of 6 subjects, the maximum observed serum LNG concentration (mean ±SD) was 302 ± 170 pg/mL, reached after 7.5 days (median) of Kyleena insertion. Thereafter, the LNG serum concentrations (mean ±SD) at Year 1, 2, 3, 4 and 5 were 199 ± 171 pg/mL (N=6), 120 ± 57 pg/mL (N=6), 122 ± 65 pg/mL (N=6), 79 ± 12 pg/mL (N=3) and 65 ± 15 pg/mL (N=3), respectively. A population pharmacokinetic evaluation based on a broader database (>1000 patients) showed a similar declining concentration profile, with 175 ± 74 pg/mL at 7 days after placement, 125 ± 50 pg/mL at 1 year, 99 ± 41 pg/mL after 3 years, and 90 ± 35 pg/mL after 5 years.

Distribution

The apparent volume of distribution of LNG is reported to be approximately 1.8 L/kg. LNG is bound non-specifically to serum albumin and specifically to sex hormone binding globulin (SHBG). Accordingly, changes in the concentration of SHBG in serum result in an increase (at higher SHBG concentration) or a decrease (at lower SHBG concentration) of the total LNG concentration in serum. In a subset of 6 subjects, the concentration of SHBG declined on average by about 30% during the first 3 months after insertion of Kyleena and remained relatively stable over the 5 year period of use. Less than 2% of the circulating LNG is present as free steroid.

Elimination

Following intravenous administration of 0.09 mg LNG to healthy volunteers, the total clearance of LNG is approximately 1 mL/min/kg and the elimination half-life is approximately 20 hours. Metabolic clearance rates may differ among individuals by several-fold, and this may account in part for wide individual variations in LNG concentrations seen in individuals using LNG–containing contraceptive products.

(b) (4)

Following absorption, LNG is extensively metabolized. The most important metabolic pathways are the reduction of the Δ4-3-oxo group and hydroxylations at positions 2α, 1β and 16β, followed by conjugation. Significant amounts of conjugated and unconjugated 3α, 5β- are also present in serum, along with much smaller amounts of 3α, 5α-tetrahydrolevonorgestrel and 16β-hydroxylevonorgestrel. CYP3A4 is the main enzyme involved in the oxidative metabolism of LNG.

Excretion

LNG and its phase I metabolites are excreted primarily as glucuronide conjugates. About 45% of LNG and its metabolites are excreted in the urine and about 32% are excreted in feces, mostly as glucuronide conjugates.

Specific Populations

Pediatric: Safety and efficacy of Kyleena have been established in women of reproductive age. Use of this product before menarche is not indicated.

Geriatric: Kyleena has not been studied in women over age 65 and is not approved for use in this population.

Race: No studies have evaluated the effect of race on the pharmacokinetics of Kyleena.

Hepatic Impairment: No studies were conducted to evaluate the effect of hepatic disease on the disposition of Kyleena.

Renal Impairment: No formal studies were conducted to evaluate the effect of renal disease on the disposition of Kyleena.

Drug-Drug Interactions

No drug-drug interaction studies were conducted with Kyleena *[see Drug Interactions (7)]*.

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/s/

LIN ZHOU
09/16/2016

MYONG JIN KIM
09/16/2016

CLINICAL PHARMACOLOGY REVIEW

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1. EXECUTIVE SUMMARY

The Applicant submitted a New Drug Application (NDA) for LCS16, a levonorgesterel (LNG) intrauterine system (IUS) containing 19.5 mg of levonorgestrel with an initial release rate of 17.5 µg/day for the indication of prevention of pregnancy for up to 5 years. LCS16 is the third LNG-IUS product the applicant is seeking approval for.

Two other LNG-IUS products, LCS12 (Skyla®) and Mirena®, are owned by the same company. Mirena® (NDA021225, approved in 2000) contains 52 mg LNG with initial *in vivo* release rate of 20 µg/day. Mirena® is approved for intrauterine contraception for up to 5 years, and for treatment of heavy menstrual bleeding in women who choose to use intrauterine contraception as their method of contraception. Skyla® (NDA 203159, approved 2013) contains 13.5 mg LNG with initial *in vivo* release rate of 14 µg/day and is indicated for prevention of pregnancy for up to 3 years. In comparison to Mirena®, LCS16 and Skyla® (LCS12) not only have lower daily release rate, but also have smaller T-frames with a silver ring for ultrasound detection.

To establish the safety and efficacy of LCS16, the applicant conducted a pivotal Phase 3 trial 310042/ PH-37274 and a supporting Phase 2 clinical study 308901/ A46796 evaluating contraceptive efficacy, bleeding patterns, as well as safety parameters.

No specific clinical pharmacology studies were conducted with LCS16. The PK and PD characterization of LCS16 up to five years is based on the Phase 3 studies, where a dense sampling scheme in a subset of women and sparse sampling in all subjects were conducted for PK characterization of LCS 16. PD characteristics included effects on ovulation, cervix, and endometrium in a subset of women in the Phase 3 studies.

1.1 Recommendations

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

1.2 Phase 4 Commitments

No Phase 4 commitments from a clinical pharmacology perspective.

1.3 Summary of Clinical Pharmacology Findings

In vivo release rate

The release of LNG from the LCS16 starts after placement in the uterine cavity. The release rate is approximately 17.5 µg/day after 24 days and is reduced to approximately 15.3 µg/day after 60 days and to 9.8 µg/day after 1 year. It then declines progressively to approximately 7.9 µg/day after 3 years and 7.4 µg/day after 5 years. The average LNG *in vivo* release rate is approximately 9 µg/day over the period of 5 years.

Absorption, Distribution, Elimination (ADE)

- Absorption

Non-compartmental analysis using data from subset population in the Phase 3 study indicated that the maximum serum concentration (Cmax) of LNG was 302 ng/L (CV = 56.3%; N=6). Cmax was reached after 7.5 days (median) with the range of 3 to 364 days. Thereafter, LNG serum concentration of LNG decreased slowly to the mean value (Cav) of 99.6 ng/L (CV =14.7%) over the 5-year duration (N=3). PK parameters obtained from the non-compartmental analysis are comparable to those derived from the population PK analysis.

- Distribution
  The apparent volume of distribution of LNG is reported to be approximately 1.8 L/kg. More than 98% of circulating LNG is protein-bound, mainly to sex hormone binding globulin (SHBG) and, to a lesser extent, serum albumin. LNG administration also affects SHBG concentrations. Data from the Phase 3 study indicated that SHBG concentration declined by about 30% during the first 3 months (N=6) after insertion of LCS16 and remained relatively stable thereafter until the end of the 5-year observation period (N=3), except that the concentration had a surge at 12 month. The sharp increase of mean concentration at 12 month was primarily driven by one subject (160735, 196.3 nmol/L at 12 month).

- Elimination (No new data related to elimination [including metabolism and excretion] of LNG submitted to this NDA. Data related to elimination of LNG were previously reviewed under the Mirena® and Skyla® NDAs.)

  Following an intravenous (iv) administration of 0.09 mg LNG to healthy volunteers, the total clearance of LNG is approximately 1 mL/min/kg and the elimination half-life is approximately 20 hours.

  - Metabolism
    Following absorption, LNG is conjugated at the 17β-OH position to form sulfate conjugates and, to a lesser extent, glucuronide conjugates in serum. Significant amounts of conjugated and unconjugated 3α, 5β-tetrahydrolevonorgestrel are also present in serum, along with much smaller amounts of 3α, 5α-tetrahydrolevonorgestrel and 16β-hydroxylevonorgestrel. LNG and its phase I metabolites are excreted primarily as glucuronide conjugates. Metabolic clearance rates may differ among individuals by several-fold, and this may account in part for wide individual variations in LNG concentrations seen in individuals using LNG–containing contraceptive products. In vitro studies have demonstrated that oxidative metabolism of LNG is catalyzed by CYP enzymes, especially CYP3A4.

  - Excretion
    About 45% of LNG and its metabolites are excreted in the urine and about 32% are excreted in feces, mostly as glucuronide conjugates.

Drug Product Formulation

- Phase 2 Formulation vs Phase 3 Formulation

  The formulations of LCS16 used in the Phase 2 and Phase 3 clinical studies were slightly different. (b) (4) Given that the safety and efficacy of LCS16 was mainly evaluated based on the Phase 3 data, the bridging between Phase 2 and Phase 3 formulations is not necessary.

- Phase 3 Formulation vs To-Be-Marketed (TBM) Formulation

  The phase 3 and TBM have the same formulation of the drug reservoir. However, compared to the phase 3 formulation, minor modifications were made to the TBM formulation, (b) (4) According to ONDP (Dr. Mark Seggel), these changes do not impact the drug reservoir or the drug release mechanism and no bridging study is needed. The compositions of LCS16 during development are presented in Table 4.

Drug-Drug Interactions (DDI)

No clinical or in vitro DDI study was conducted under this NDA. Contraceptive effect of Kyleena is mediated via the direct release of LNG into the uterine cavity and thus is unlikely to be affected by drug interactions via enzyme induction or inhibition.

Specific Populations

- Renal/hepatic impairment

  No formal studies have evaluated the effect of renal or hepatic disease on the disposition of LNG released fromLCS16. Theoretically, serum concentration of LNG could be elevated in women with impaired renal or hepatic function. However, the average daily dose (release rate) of LCS16 over 5 years is, more than 10 times and initially more than 5 times lower than the doses that are given during the treatment with combined oral contraceptives. Thus, no critical concentrations are expected during the use of LCS16 in women with renal or hepatic impairment.

Bioanalytical Method Validation

Validated analytical methods were used in clinical studies. Acceptance criteria and assay performance for each analyte were in compliance with the Bioanalytical Method Validation Guidance and therefore found to be acceptable.

2. QUESTION BASED REVIEW

2.1 General Attributes

2.1.1 What is LCS 16?

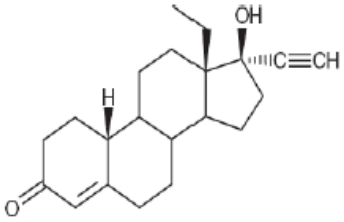
LCS16 (Kyleena^{TM}) is a LNGIUS containing 19.5 mg LNG for the proposed indication of prevention of pregnancy for up to 5 years. LCS16 consists of a hormone-elastomer reservoir mounted on the T-

shaped polyethylene frame (T-body). The reservoir is covered by a polydimethylsiloxane (PDMS) membrane [redacted (b) (4)]. The *in vivo* release rate is estimated to be 17.5 µg/day after 24 days. This rate decreases progressively to 9.8 µg/day after 1 year and to 7.4 µg/day after 5 years. The average *in vivo* release rate of LNG is approximately 9 µg/day over a period of 5 years.

2.1.2 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

Active substance

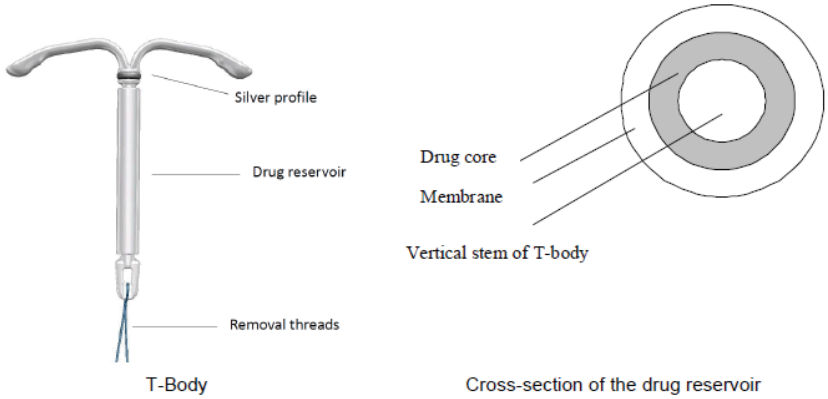
The active pharmacologic ingredient in LCS16 is LNG. LNG USP is a white [redacted (b) (4)] powder chemically described as (-)-13-Ethyl-17-hydroxy-18,19-dinor-17α-pregn-4-en-20-yn-3-one. It has a molecular weight of 312.4, a molecular formula of $C_{21}H_{28}O_2$, and the following structural formula:



Formulation

Kyleena consists of a T-shaped polyethylene frame (T-body) with a steroid reservoir (hormone elastomer core) around the vertical stem. The white T-body has a loop at one end of the vertical stem and two horizontal arms at the other end. The reservoir consists of a whitish or pale yellow cylinder, made of a mixture of LNG and silicone (polydimethylsiloxane), containing a total of 19.5 mg LNG. The reservoir is covered by a semi-opaque silicone membrane, composed of polydimethylsiloxane and colloidal silica. A ring composed of 99.95% pure silver is located at the top of the vertical stem close to the horizontal arms and is visible by ultrasound. The polyethylene of the T-body is compounded with barium sulfate, which makes it radiopaque. A monofilament blue polypropylene removal thread is attached to a loop at the end of the vertical stem of the T-body. The polypropylene of the removal thread contains <0.5% phthalocyaninato(2-) copper as a colorant (see Figure 1).

Figure 1. Schematic illustration of the system



2.1.3 What is the proposed mechanism of action and therapeutic indications(s)?

The contraceptive effect of LCS16 is mainly achieved via local progestogenic effect within the uterine cavity and cervix, including thickening of cervical mucus preventing passage of sperm into the uterus, inhibition of sperm capacitation or survival, and alteration of the endometrium. The proposed indication for Kyleena is prevention of pregnancy for up to 5 years.

2.1.4 What are the clinical and clinical pharmacology data submitted to support the approval of LCS16?

To establish the safety and efficacy of LCS16, the applicant conducted a pivotal phase 3 trial 310442/ PH-37274 and a supporting Phase 2 clinical study 308901/ A46796 evaluating contraceptive efficacy, bleeding patterns, as well as safety parameters (Table 1).

The pivotal Phase 3 trial was a multicenter, open-label, randomized study to assess the safety and contraceptive efficacy of LCS12 and LCS16 for originally a maximum of three years, but extended up to five years (extension phase) for LCS16. In this study, a total of 1452 women from 18-35 years old were assigned for LCS16 assessment and 707 subjects continued in the extension phase (after year 3). From these, 550 subjects completed study at year 5. Majority (80.2%) of the 1452 women were Caucasian, 11.0% were Hispanic, 5.1% were black, 1.2% were Asian and 2.6% were reported as other. The mean age of subjects was 27.1 years, the mean weight was 68.7 kg and the mean BMI was 25.32 kg/m^2 (overweight: 25.4%, obese 15%, and severe obese 2.2%). This trial was conducted in the US under IND 073505. Trial 310442/ PH-37274 (5-year data) and population PK analysis report (R-9266, based on data from 310442/PH-37274) were reviewed in details because they provide clinical pharmacology information related to the 5-year use of LCS16.

The Phase 2 Study 308901/A46796 was a multicenter, open-label, randomized, dose finding study to investigate LCS12 and LCS16 compared to Mirena® for a maximum of 3 years. Data from Study 308901/A46796 were used to develop the population PK model for LNG and were reviewed in NDA 203159 for Skyla® and are not reviewed in details again in this NDA. One thing to be noted, the phase 2 formulation contains only (b) (4) mg of LNG while the phase 3 formulation contains 19.5 mg of LNG.

Table 1. Clinical studies/reports support the approval of LCS16.

Studies/Reports in which LCS16 were tested		
Study No.	**Study Design**	**Main objectives regarding to PK/PD parameters**
308901/A46796 (Phase 2, Europe)	Multicenter, randomized, open-label, 3-arm (LCS12, LCS16 and Mirena®) parallel group dose finding study for 3 years	• PD: Ovarian, cervical function and hormone concentrations (n=15 for LCS16); endometrial history (n=28 for LCS16) • PK of LNG and SHBG (n=12 for LCS 16)
310442/PH-37274 (Phase 3, Europe, US, Canada, Latin America)	Multicenter, randomized, open, 2 arm (LCS12 and LCS16), parallel group 3 years (up to 5 years for LCS16 only)	• PD: Ovarian, cervical function and hormone concentrations (n=19 for LCS16); endometrial history (n=30 for LCS16) • PK of LNG and SHBG, serum silver ion concentration (n = 13 for LCS16)
R-9266 (modeling and simulation)	Population PK Evaluation (serum concentrations and release rate of LCS16) of phase 3 Efficacy study 310442/PH-37274 (5 years)	• Characterize the population PK of LNG in the LCS16 treatment arm over the period of 5 years in study 310442/PH-37274 • Investigate the impact of covariates (body weight and age) on clearance of LCS16

		• Estimate individual total and unbound LNG serum concentration (1 month, 3 months, 1 year, 2 years, 3 years, 4 years, 4.5 years and 5 years) • Estimation of LNG in vivo release rates (24 days and 60 days after insertion, 1, 3, 4, 4.5 and 5 years after insertion) and the 5-year average rate.

No specific clinical pharmacology studies were conducted with LCS16. The PK and PD characterization of LCS16 up to five years is based on the Phase 3 trial 310442/37274 where a dense sampling scheme in a subset of women was conducted to determine non-compartmental PK parameters of LNG after LCS16 insertion. In the same trial, a sparse sampling scheme (one sample per subject) was conducted in all subjects treated with LCS16 for a population PK analysis using serum concentration data of LNG and the binding protein, SHBG. PD characteristics including effects on ovulation, cervix, in a subset of women in the Phase 3 study. PD data were reviewed by Clinical reviewer.

The applicant submitted reports for two Phase 3 trials (Trial 14371/PH-37275 and 91775/37272), in which only LCS12 was studied. Also the applicant submitted two population PK analysis reports (R-8893 and PH-37542) which were based on these two phase 3 trials. Trial 14371/PH-37275 assessed the efficacy, safety, bleeding pattern and PK of LCS12 in women from the Asian-Pacific region. Trial 91775/37272 investigated the efficacy, safety, bleeding pattern and PK of LCS12 in post-menarcheal female adolescents under 8 years of age. (b) (4)

In addition, several supplementary studies were included in the submission to inform PK of LNG from IUS, protein binding of LNG, and in vitro drug interactions and metabolism of LNG. These studies had been reviewed under NDA 203159 for Skyla® (LCS12).

2.2 General ClinicalPharmacology

2.2.1 Is the proposed dose and dosing regimen acceptable?
Yes. In the clinical development program of this product, the efficacy and safety of LCS16 up to 5 years were demonstrated in the pivotal phase 3 trial (310442/PH-37274).

2.2.2 What is the *in vivo* release rate of LNG from LCS 16?
In order to characterize the in vivo performance of LCS16, in vivo release rates were calculated based on ex vivo residual content and plasma concentration data obtained from women who prematurely discontinued or completed the study treatment in the pivotal phase 3 trial 310442/PH-37274. A population PK model was used to calculate in vivo release rates over the entire 5 years of use.

Based on the population PK approach, the in vivo release rate of LCS16 was 17.5 µg/day at day 25 and declined to 9.79 µg /day at 1 year and 7.89 µg/day at 3 years after insertion. Thereafter, the release rate remained relatively stable until the end of year 5 (7.44 µg/day). The calculated average release rate over the entire time of LCS16 use was 8.99 µg/day. Per ONDP reviewer Dr. Hansong Chen, the estimated *in vivo* release rates are acceptable.

2.2.3 What are the PK characteristics of LCS16?

No dedicated PK study was conducted for LCS16. The Phase 2 study (308901/A46796) was conducted with a different formulation while the Phase 3 and TBM formulations are deemed the same. Therefore, only the PK data of the TBM product is described. Based on the data from the phase 3 trial (310442/ PH-37274), the PK of LCS16 was characterized using the following:

- Non-compartmental analysis: a dense sampling scheme in a subset of women

For the PK subset (also called "Subset 3" in the study report), 12 planned, 11 enrolled, 6 remaining after year 3. These 6 subjects were given the option to enter extension phase, 3 out of the 6 subjects entered the extension phase and completed the five-year trial.
PK parameters for LCS16 estimated from non-compartmental analysis are summarized in Table 2. For all PK parameters, the arithmetic means with the coefficient of variation (CV, in parentheses) are given, except for Tmax, Tmin and Tlast, where the median and the range (in parentheses) are provided.

After insertion of LCS16, the arithmetic mean of maximum serum concentration (Cmax) of LNG was 302 ng/L (CV = 56.3%; N=6). Cmax was reached after 7.5 days (median) with the range of 3 to 364 days). For the complete treatment period of 5 years (N=3), the systemic exposure ($AUC_{0\text{-}tlast}$) had an arithmetic mean value of 180488 ng/L·day (CV=11.8%) and the average concentration (Cav, calculated as $AUC_{0\text{-}tlast}/T_{last}$) had an arithmetic mean value of 99.6 ng/L (CV =14.7%). Minimum concentrations (Cmin, arithmetic mean 60.6 ng/L, CV=14%) were reached towards the end of the study after about 5 years.

Table 2. Arithmetic Mean (%CV) PK parameters of LNG observed after insertion of LCS16 over the 5-year period (N=3) and the 3-year period (N=6) in the phase 3 trial (PH-37274).

	C_{max} (ng/L)	T_{max} (d)	C_{min} (ng/L)	T_{min} (d)	C_{last} (ng/L)	T_{last} (d)	$AUC_{(0\text{-}last)}$ (ng*d/L)	C_{av} (ng/L)
LCS16 5-years N=3	220 (30.7%)	4 (3-8)	60.6 (14%)	1788 (1650-1819)	65.1 (22.5%)	1819 (1788-1832)	180488 (11.8%)	99.6 (14.7%)
LCS 16 3-years N=6	302 (56.3%)	7.5 (3-364)	93.5 (43.4%)	559 (385-916)	122.3 (53.4%)	1086 (1084-1096)	153168.7 (50.1%)	140.8 (50.2%)

- Population PK analysis: a sparse sampling scheme at one sample per subject

Previously, a population PK model was developed using the Phase 2 study 308901/A46796 and Phase 1 study 92085 (Report No.:A57551) data of LCS12 and it was subsequently refined using the phase 3 trial 310442/A52238 of LCS12 (data up to 3 years of treatment only; Report No: A57552). Both reports were reviewed by Dr. Li Li for the approval of Skyla® (LNG IUS, LCS12, Bayer, NDA 203159) in year 2012 and found to be acceptable from a clinical pharmacology perspective (Dr. Li Li's Clinical Pharmacology review dated 12/05/16 under NDA 203159).

The previously developed population PK model which was then optimized in the present analysis (final model). Based on the final model, total and unbound LNG concentrations were estimated for all subjects with at least one valid PK measurement (LNG or SHBG serum concentration above the LLOQ or a residual content measure).

The mean serum concentrations of total LNG decrease slowly from average concentrations (%CV) at 1 month of 164 (39.1%) ng/L to average concentrations at 5 years of 89.7 (39.3%) ng/L. The predicted mean of unbound LNG decreases from 2.42 (24.5%) ng/L at 1 month to 1.27 (24%) ng/L at 5 years of treatment (only about 1.5% of total LNG is unbound). Please see the appended R-9266 study report review for the summary statistics of the total and unbound LNG concentrations for the complete study population.

2.2.4 What are the ADME characteristics of LNG released from LCS16?
The ADME of LNG after release from Kyleena is described in Section 1.3.

2.2.5 Is there a depot effect after LCS16 removal?
Not likely. No study was conducted to measure the LNG serum concentration after LCS16 removal. However, there was no sign of a depot effect with Mirena® (a higher-dose product). Specifically, the data from study A10982 showed that LNG concentrations declined immediately (within 1 day) after Mirena® removal, and were undetectable at 7 days after removal.

2.3 Intrinsic Factors

2.3.1 What intrinsic factors (age, race, weight, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

Relationship between Body Weight and Exposure/Contraceptive efficacy and safety
Based on the population PK analysis, the impact of body weight on LNG clearance was significant. Clearance (CL/F) increased linearly by 0.84% per kg body weight for the body weight range within trial 310442/PH-37274 (39 to 160 kg, median 65 kg with corresponding CL/F values of 188-432 L/h for the range and 240 L/h for the median, respectively). Due to the effect of body weight on the clearance of LNG, the LNG exposure is higher for lower body weights.

In the pivotal phase 3 trial 310442/ PH-37274, 250 women had BMI over 30 kg/m^2 and 1198 women had BMI lower than 30 kg/m^2 (Table 3). Although the Pearl Index (PI) in women with BMI $\geq$ 30 kg/m^2 was higher than that in women with BMI lower than 30 kg/m^2, 0.56 vs. 0.24, BMI subgroups are too small (overlapping CIs) to show differences in efficacy of Kyleena, per clinical reviewer Dr. Ronald Orleans.

Note: The PI is the primary variable and defined as number of unintended pregnancies per 100 woman years.

Table 3. Cumulative (5-year) analysis of PI by subgroup – All subjects treated with LCS16 in the phase 3 trial, 310442/PH-37274. (Source: Table 9-2 of Amended Clinical Study Report PH—37274, page 84/162)

	N women / n pregnancies	Relevant exposure time (WY)	Pearl index	Lower; Upper 95% CI
Cumulative 5-year PI				
All women	1452 / 13	4434.53	**0.29**	0.16; 0.50
By Age				
18-25 years	564 / 3	1628.02	**0.18**	0.04; 0.54
>25-35 years	888 / 10	2806.51	**0.36**	0.17; 0.66
By Parity				
Nulliparous	574 / 4	1636.24	**0.24**	0.07; 0.63
Parous	878 / 9	2798.28	**0.32**	0.15; 0.61
By BMI				
<30 kg/m²	1198 / 9	3701.88	**0.24**	0.11; 0.46
≥30 kg/m²	250 / 4	720.57	**0.56**	0.15; 1.42

BMI = Body mass index; CI = confidence interval; FAS = full analysis set; N = number of subjects; PI = Pearl index; WY = women years.
Source: Table 14.2.1/1, Table 14.2.1/2, Table 14.2.1/3 and Table 14.2.1/4.

Relationship between Renal/Hepatic Impairment and Exposure

No formal studies have evaluated the effect of renal or hepatic disease on the disposition of LNG released from LCS16.

Theoretically, serum concentration of LNG could be elevated in women with impaired renal or hepatic function. However, the average daily dose (release rate) of LCS16 over 5 years is, more than 10 times and initially more than 5 times lower than the doses that are given during the treatment with combined oral contraceptives. Thus, no critical concentrations are expected during the use of LCS16 in women with renal or hepatic impairment.

2.4 Extrinsic Factors

No clinical or in vitro DDI study was conducted under this NDA. Contraceptive effect of Kyleena is mediated via the direct release of LNG into the uterine cavity and thus is unlikely to be affected by drug interactions via enzyme induction or inhibition.

2.5 General Biopharmaceutics

2.5.1 Is the clinical trial formulation same as the to-be-marketed (TBM) formulation?

No. Compared to the phase 3 formulation, minor modifications were made to the TBM formulation, (b) (4) According to ONDP (Dr. Mark Seggel), these changes do not impact the drug reservoir or the drug release mechanism and no bridging study is needed. In addition, the phase 3 and TBM have the same formulation of the drug reservoir. The compositions of LCS16 during development are presented in Table 4.

The formulations of LCS16 used in the Phase 2 and Phase 3 clinical studies were slightly different. (b) (4)

[redacted] Given that the safety and efficacy of LCS16 was mainly evaluated based on the Phase 3 data, the bridging between Phase 2 and Phase 3 formulations are not necessary.

Table 4. The clinical trial and TBM formulations of LCS16

Component/description	Phase 2	Phase 3	TBM
Drug core LNG content	[redacted]	19.5 mg	19.5 mg
Core [redacted] Material	PDMS elastomer core	PDMS elastomer core	PDMS elastomer core
Membrane [redacted] Membrane thickness target Material	PDMS silica [redacted]	PDMS silica [redacted]	PDMS silica [redacted]
[redacted] **drug core** Length	[redacted]	19 mm	19 mm
T-body Composition Dimension Length of horizontal arm x vertical stem x diameter of vertical stem Silver profile	[redacted] - -	[redacted] 28 x 30 x [redacted] mm [redacted]	[redacted] 28 x 30 x [redacted] mm [redacted]
Removal thread Composition Dimensions	[redacted]	[redacted]	[redacted]
Inserter Insertion applicator	inserter	inserter	LCS [redacted] inserter

PDMS = poly (dimethylsiloxane)
Source (Table 1-1 of Module 2.7.1 of the submission)

2.6 Analytical Section

2.6.1 What bioanalytical methods are used to assess concentrations?
There have been no updates to the methods for determining LNG and SHBG serum concentrations since the approval of Skyla® (LCS12).

LNG serum concentration
LNG serum concentrations were determined with a validated radioimmunoassay (RIA) method based on the specific antiserum preparation and tritium labeled LNG. The detailed analytical conditions are summarized in Table 5.

All samples were stored at or below -15 ºC (nominally -20 ºC) and analyzed within four years after sampling, most of them within two years after sampling.

Details of the method description and validation can be found in study report A01291 revised version 3 "Determination of LNG by RIA and SHBG by TR-FIA from A52238/310442."

Table 5. RIA for serum LNG concentration

Calibration Range	10 to 2000 ng/L
Lower limit of quantitation (LLOQ)	30 ng/L
Upper limit of quantitation (ULOQ)	600 ng/L
Inter-assay Standard Precision (% CV)	≤ 4.3 %
Inter-assay Standard Accuracy (% Bias)	98.0 to 102.0 %
Accuracy at LLOQ	99%
Precision at LLOQ	6.4%
Inter-assay QC Precision (% CV)	6.8 to 14.0%
Inter-assay QC Accuracy (% Bias)	90.0 to 102.0%
Stability in plasma at or below -15 ºC (nominally -20 ºC)	715 days
Incurred sample stability at or below -15 ºC (nominally -20 ºC)	1383 days (<4 years) A long term stability of LNG in human serum sample stored at or below -15 ºC for at least 4 years was measured in a partial validation study 2011033*

*Report for study 2011033 (R-11086) was submitted on 06/16/16 in response to our information request Sent to the Applicant on 06/07/16 via email.

Report R-11086 provided the results of the long-term stability experiments for samples stored at a nominal temperature of -20°C for 1, 2, 3, and 4 years. The following concentrations were tested and are listed together with the acceptance ranges of ±15% of the nominal value:

Stability samples (ng/L)	**49.4**	**197**	**494**
Acceptance range (ng/L)	42.0-56.8	167-227	420-568

Stability is demonstrated for a period of storage of at least 1,100 days for all concentrations. Stability is also demonstrated for a period of storage of at least 1,478 days for all concentrations at and above 197 ng/L. The low concentration tested did not fulfill the ± 15% acceptance criteria, as the sample concentration was experimentally determined to be 126% of the nominal concentration. We found the validation report to be adequate for the following reasons:

1. The number of samples affected was very small. In the phase 3 trial 310442, only 12 out of 4299 samples analyzed (9 LCS16 samples and 3 LCS12 samples) were stored for more than 1,100 days, which corresponds to 0.28% of the total number of samples analyzed. Of these, one concentration was below the lower limit of quantitation, and another one was determined to be above 197 ng/L. The 10 remaining samples (7 LCS16 samples and 3 LCS12 samples) had concentrations between 47.1 and 182 ng/L.
2. Over reporting of PK concentration of these 10 samples by ~11% (126-115%) is not expected to have an impact on the safety or efficacy of the product.

SHBG serum concentration

The concentration of SHBG in human serum was determined with a time-resolved fluoroimmunoassay (TR-FIA). The detailed analytical conditions are presented in Table 6.

All samples were stored at or below -15°C (nominally -20°C) and analyzed within four years after sampling, most of them within two years after sampling.

Details of the method description and validation can be found in study report A01291 revised version 3 "Determination of LNG by RIA and SHBG by TR-FIA from A52238/310442."

Table 6. TR-FIA for serum SHBG concentration

Calibration Range	6.30 to 200 nmol/L
Lower limit of quantitation (LLOQ)	9.80 nmol/L
Upper limit of quantitation (ULOQ)	197 nmol/L
Inter-assay Standard Precision (% CV)	≤ 1.4 %
Inter-assay Standard Accuracy (% Bias)	99 to 101 %
Accuracy at LLOQ	100%
Precision at LLOQ	0.4%
Inter-assay QC Precision (% CV)	2.4 to 7.3 %
Inter-assay QC Accuracy (% Bias)	89% to 111 %
Stability in plasma at or below -15 ºC (nominally -20 ºC)	6 years and 8 months

(b) (4)

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4. APPENDIX

4.1 Individual Study Review

4. 1.1 Review for Phase III trial 310442/PH-37274
(Review focuses on LCS16 PK characterization with non-compartment analysis)

Multi-center, open-label, randomized study to assess the safety and contraceptive efficacy of two doses (in vitro 12 mcg/24 h and 16 mcg/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 mcg/24 h dose group (LCS16 arm) up to 5 years

Protocol Number:	PH-37274
Phase:	3
Principal Investigator:	138 principal investigators at 138 recruiting study centers. 109 centers continued in the extension phase (extension of LCS16 treatment).
Clinical Study Centers:	Argentina (5), Canada (13), Chile (3), Finland (15), France (8), Hungary (8), Mexico (4), Netherlands (9), Norway (5), Sweden (11), USA (57)
Clinical Study Dates:	08/20/2007-06/07/2013

BACKGROUND:
No dedicated clinical pharmacology study was conducted with LCS16. The characterization of LCS16 PK profile was mainly based on the phase 3 trial by non-compartmental analysis via intense PK sampling in a subset of subjects and by population PK analysis via sparse sampling of one measurement per subject. The population PK analysis was reviewed separately in the population PK study report R-9266. Therefore, the current individual study review mainly focused on non-compartmental analysis of LCS16 using data from the 6 subjects.

OBJECTIVE:
Characterization of the PK profile of LNG released from LCS16 over 5 years.

STUDY ENDPOINTS:
PK parameters including C_{max}, C_{av}, C_{min}, C_{last}, T_{max}, T_{last}, T_{min} and AUC $_{(0\text{-}Tlast)}$ for LNG

STUDY DESIGN, TREATMENT AND SUBJECTS
Trial 310442/PH37274 was the pivotal LCS16 efficacy trial with regards to the efficacy and safety assessment of LCS16. It was a large, multicenter, randomized, open-label, 2-arm, parallel-group, phase 3 trial to investigate the efficacy and safety of the two doses of LCS, LCS12 and LCS16, for a maximum of three years in nulliparous and parous women. The women in the LCS16 group were given the option to continue into an extension phase (single arm, open-label) with treatment up to 5 years.

Twenty-four (24) subjects were planned for the PK subset study (also called Subset 3 in the protocol) with 12 subjects per treatment arm (LCS12 and LCS16). One LCS with either 12 mcg/day (LCS12) or 16 mcg/day (LCS16) LNG initial in vitro daily release rate was inserted into each subject. After a successful insertion, the LCS was to remain in the uterine cavity until its removal at the end of the study or on premature discontinuation of the subject from the study.

For the LCS 16 arm, blood samples for determination of serum LNG and SHBG were taken at the following time points:

- First 3 year study: at baseline (prior to LCS16 insertion), after the start of the study treatment day 1 (+1 day), day 3 and day 7 (±1 day), day 14 (±2 days), 3 months (±1 week), 6 months and 9 months, 1, 1½, 2 and 2½ years (±4 weeks). A sample was also taken at the end of study treatment prior to LCS removal (end-of-study visit / 3 years [- 2 weeks] from those subjects t who did not participate in the extension phase.
- Extension phase: at 3, 3½, 4 and 4½ years (±4 weeks) and always at the end of study treatment prior to LCS removal at the end–of-study (EOS) visit /5 years (-2 weeks).

Twenty-three subjects were enrolled into in the PK subset study (12 for LCS 12 arm and 11 for LCS16 arm). Subjects who had no 3-year LNG and SHBG samples, or more than one missing sample around tmax were excluded from the interim PK analysis at end of year 3 (based on Clinical Study Report of A52238). Thus, only 13/23 subjects were included for the 3-year pharmacokinetic analysis, 7 subjects from treatment arm LCS12 and 6 subjects from treatment arm LCS16. The remaining 6 subjects in LCS16 arm were given the option to enter extension phase, 3 out of the six subjects entered the extension phase and completed the five-year trial.

FORMULATION

Generic name:	Levonorgestrel (LNG) BAY 86-5028						
Treatment	Formulation number (SH)	Initial *in vitro* release rate of LNG (µg/day)	Total LNG content (mg)	Dimensions of the LCS (mm)	Drug reservoir diameter (mm)	Drug reservoir length (mm)	Inserter diameter (mm)
LCS16:	G04209G	16	19.5	28 x 30	[redacted] (b) (4)		3.80
Type of formulation	Intrauterine system (IUS)						
Route of administration	Intrauterine						
Sterile product	Yes [sterilized with ethylene oxide]						
Description of the pharmaceutical preparation	The LCS consists of a polyethylene T-shape frame with a drug reservoir cylinder around the vertical stem. This reservoir consists of a mixture of polydimethyl-siloxane and LNG covered by a polydimethylsiloxane membrane [redacted] (b) (4) [redacted] (b) (4) The T-shaped frame has flexible, curved, horizontal arms and a vertical arm that have overall lengths as provided above. The frame is impregnated with barium sulfate to make the system X-ray detectable. On top of the vertical arm, [redacted] (b) (4) [redacted] (b) (4) a thin silver ring is placed to facilitate detection by ultrasound. Removal threads are tied to the loop at the low-end of the vertical arm of the system. The period of use for LCS16 is targeted to be 5 years.						
Packaging	The LCS is packed [redacted] (b) (4) with a specially designed inserter. The primary package is packed in a secondary cardboard package.						
Units per package	1						
Manufacturer of the pharmaceutical preparation	Bayer Oy, Turku, Finland						
Manufacturer of the substance bulk ware	Bayer AG, [redacted] (b) (4)						

Source: Table 7-1 of the clinical study report

BIOANALYTICAL METHOD

Serum concentrations of LNG and SHBG were analyzed in (b) (4). Samples taken after year 3 were analyzed by the same assay at the same labs.

- Determination of LNG in serum

LNG was determined in human serum with an RIA method based on the specific antiserum preparation and tritium labeled LNG. The serum samples were extracted with diethyl ether, phase separation was achieved by centrifugation and by freezing the aqueous layer. Separation of the antibody-bound LNG from unbound was achieved by charcoal suspension. The radioactivity (^{3}H-LNG) was measured by means of scintillation counter.

All samples were stored at or below -15 ºC (nominally -20 ºC) and analyzed within four years after sampling, most of them within two years after sampling.

The detailed analytical conditions are presented in Table 1. Details of the method description and validation can be found in study report A01291 revised version 3 "Determination of LNG by RIA and SHBG by TR-FIA from A52238/310442."

Table 1 RIA for serum LNG concentration

Calibration Range	10 to 2000 ng/L
LLOQ	30 ng/L
ULOQ	600 ng/L
Inter-assay Standard Precision (% CV)	≤ 4.3 %
Inter-assay Standard Accuracy (% Bias)	98.0 to 102.0 %
Accuracy at LLOQ	99%
Precision at LLOQ	6.4%
Inter-assay QC Precision (% CV)	6.8 to 14.0%
Inter-assay QC Accuracy (% Bias)	90.0 to 102.0%
Stability in plasma at or below -15 ºC (nominally -20 ºC)	715 days
Incurred sample stability at or below -15 ºC (nominally -20 ºC)	1383 days (<4 years) A long term stability of LNG in human serum sample stored at or below -15 ºC for at least 4 years was measured in a partial validation study 2011033* (submitted on 06/16/2016).

*Report for study 2011033 was submitted on 06/16/16 in response to our information request sent on 06/07/16 via email.

- Determination of SHBG in serum

The concentration of SHBG in human serum was determined by means of a commercially available 96-well plate TR-FIA obtained from (b) (4)

All samples were stored at or below -15°C (nominally -20°C) and analyzed within four years after sampling, most of them within two years after sampling.

The detailed analytical conditions are presented in Table 2. Details of the method description and validation can be found in study report A01291 revised version 3 "Determination of LNG by RIA and SHBG by TR-FIA from A52238/310442."

Table 2. TR-FIA for serum SHBG concentration

Calibration Range	6.30 to 200 nmol/L
LLOQ	9.80 nmol/L
ULOQ	197 nmol/L
Inter-assay Standard Precision (% CV)	≤ 1.4 %
Inter-assay Standard Accuracy (% Bias)	99 to 101 %
Accuracy at LLOQ	100%
Precision at LLOQ	0.4%
Inter-assay QC Precision (% CV)	2.4 to 7.3 %
Inter-assay QC Accuracy (% Bias)	89% to 111 %
Stability in plasma at or below -15 ºC (nominally -20 ºC)	6 years and 8 months

DATA ANALYSIS

The PK parameters of Cmax, Cav, Cmin, Clast,Tmax, Tlast, Tmin and AUC0-tlast for LNG were calculated using the model-independent (compartment-free) method. *The sponsor reported geometric means of majority of PK parameters. In order to report the arithmetic mean of all the PK parameters, the reviewer ran all the analysis again using Phoenix 64* (b) (4)

RESULTS

- **Serum LNG concentration**

PK parameters for LCS16 and LCS12 are summarized in Table 3. For all PK parameters, the arithmetic mean with the coefficient of variation (CV, in parentheses) are given, except for Tmax, Tmin and Tlast, where the median and the range (in parentheses) are provided. The concentrations time profile over the completed period of 5-years (LCS16) and 3-years (LCS12) and for the first 3 months after insertion (LCS 12 and LCS 16) is shown in Figure 1.

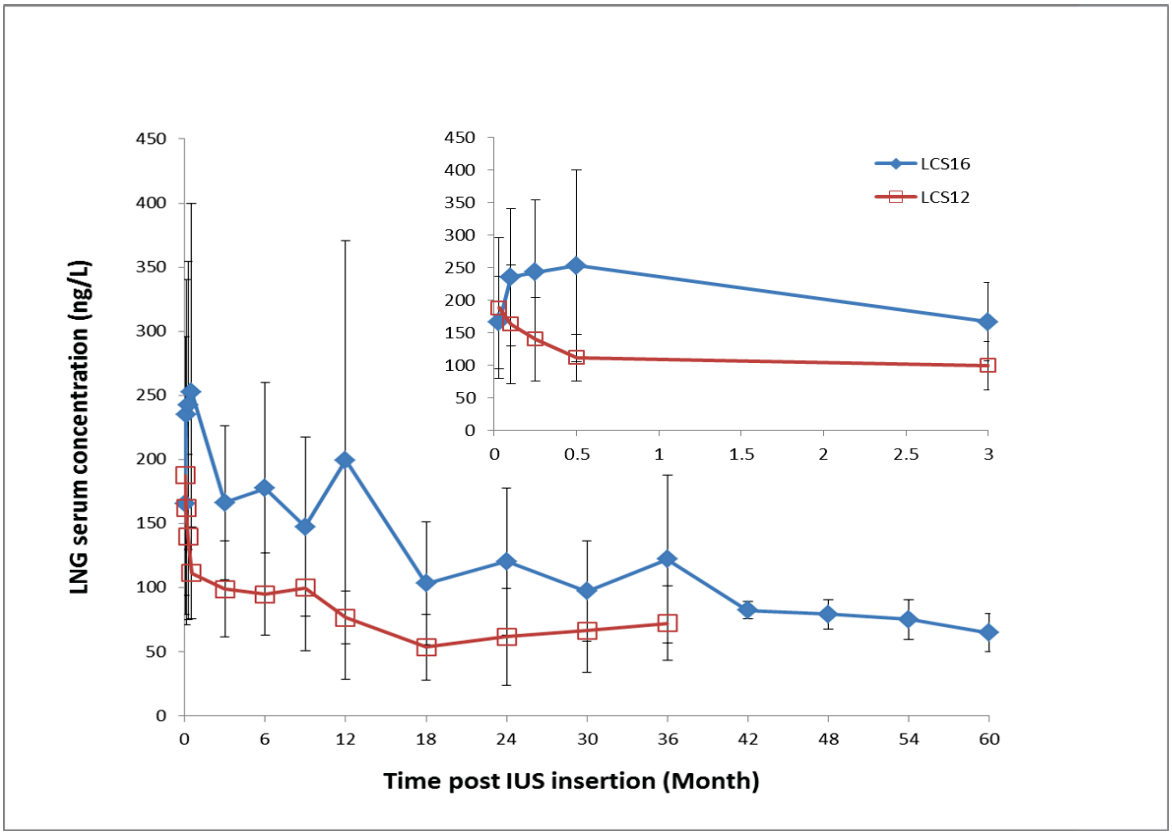
After insertion of LCS16, the arithmetic mean of Cmax of LNG was 302 ng/L (CV = 56.3%; N=6). Cmax was reached after 7.5 days (median) with the range of 3 to 364 days. For the complete treatment period of 5 years (N=3), the systemic exposure ($AUC_{0\text{-}tlast}$) had an arithmetic mean value of 180488 ng/L·day (CV=11.8%) and the average concentration (Cav, calculated as $AUC_{0\text{-}tlast}/T_{last}$) had an arithmetic mean value of 99.6 ng/L (CV =14.7%). For Cmin, an arithmetic mean 60.6 ng/L (CV=14%, N=3?) was reached towards the end of the study after about 5 years.

Table 3. Arithmetic Mean (%CV) PK parameters of LNG observed after insertion of LCS16 over the 5-year period (N=3) and of LCS16 and LCS12 over the 3-year period (N=6 [LCS16], N=7 [LCS12]) in the phase 3 trial 310442/PH-37274.

	C_{max} (ng/L)	T_{max} (d)	C_{min} (ng/L)	T_{min} (d)	C_{last} (ng/L)	T_{last} (d)	$AUC_{(0\text{-}last)}$ (ng*d/L)	C_{av} (ng/L)
LCS16 5-years N=3	220 (30.7%)	4 (3-8)	60.6 (14%)	1788 (1650-1819)	65.1 (22.5%)	1819 (1788-1832)	180488 (11.8%)	99.6 (14.7%)
LCS 16 3-years N=6	302 (56.3%)	7.5 (3-364)	93.5 (43.4%)	559 (385-916)	122.3 (53.4%)	1086 (1084-1096)	153168.7 (50.1%)	140.8 (50.2%)
LCS 12 3-years N=7*	191.7 (54.6%)	2 (1-16)	47.9 (62.7%)	733 (546-1085)	72.5 (40.1%)	1085 (1083-1135)	82594.1 (42%)	75.8 (42.4%)

*include 2 subjects each with one concentration value < LLOQ (PID160734 and PID160753) which were set to ½ LLOQ for evaluation.
$AUC_{0\text{-}tlast}$ = area under the drug concentration vs time curve from time 0 to 3 years after insertion or to until removal of the IUS at 5 years after insertion;
C_{av} = average steady state concentration ($AUC_{0\text{-}Tlast}/T_{last}$);
C_{last} = last observed concentration;
C_{min} = minimum observed concentration;
C_{max} = maximum observed concentration;
CV= coefficient of variation;
d = day;
N= number of subjects;
T_{last} = time to reach C_{last}; T_{min} = time to reach C_{min}; T_{max} = time to reach C_{max}.

Figure 1. Arithmetic mean concentrations of LNG (ng/L) in serum after insertion of LCS16 over the complete study period of 5 years (N=6 for 3 years and N=3 for 5 years) and over 3 years for LCS12 (N=7) in the phase 3 trial (PH-37274, large graph: up to 5 years, small graph: first 3 months after insertion)



- **Serum SHBG concentration**

SHBG concentrations for LCS16 and LCS12 are summarized in Table 4. For all concentrations, the arithmetic mean values with %CV are given. The concentration time profile over the completed period of 5-years and for the first 3 months after insertion is shown in Figure 2.

After insertion of LCS16, mean SHBG serum concentrations declined from 96.1 (45.2%) nmol/L at baseline to 67.1 (50.9%) nmol/L at 3 months after insertion. The SHBG concentrations remain relatively stable thereafter until the end of the 5-year observation period, except that the concentration had a surge at 12 month. The sharp increase of mean concentration at 12 month was primarily driven by one subject (160735, 196.3 nmol/L at 12 month).

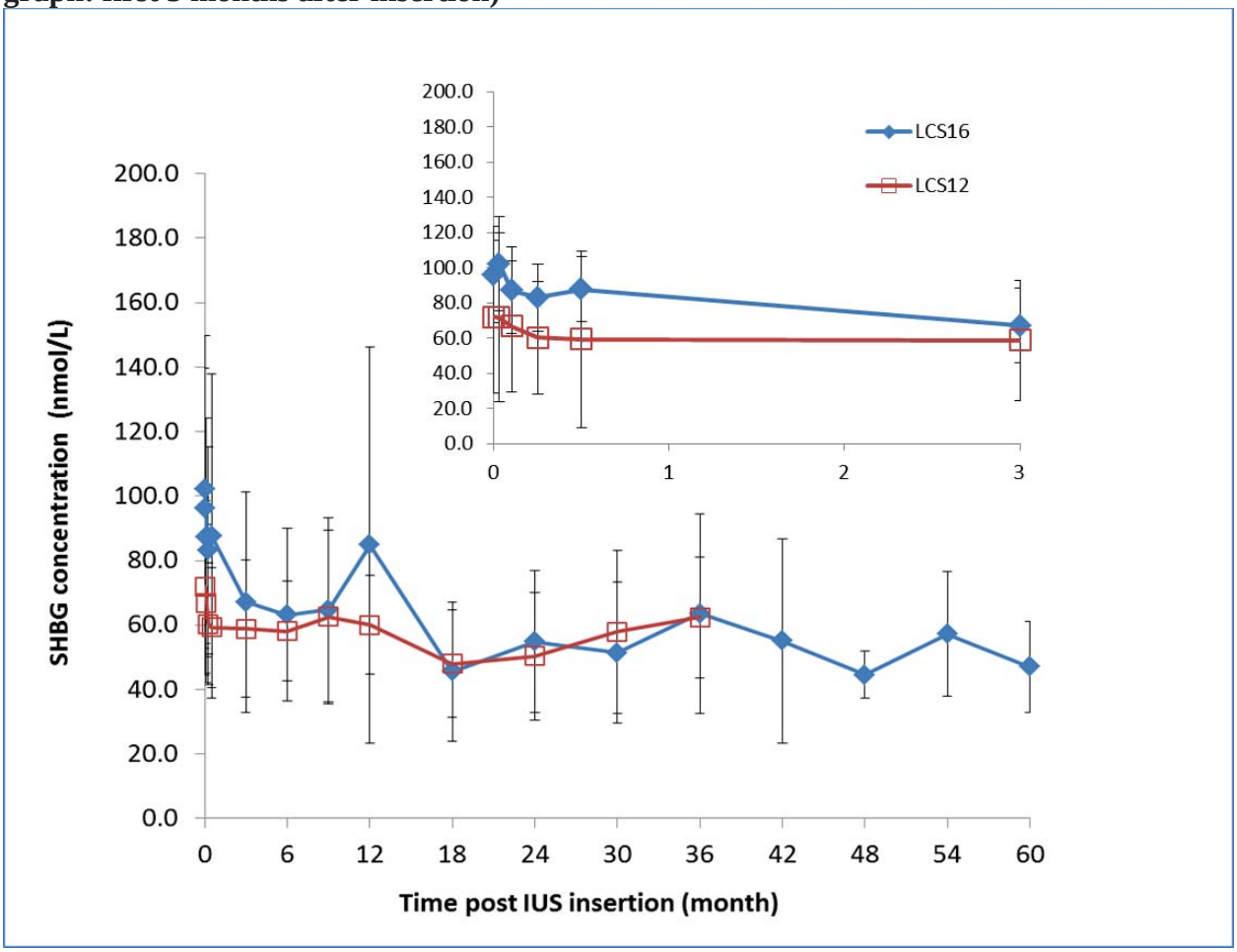
After insertion of LCS12, SHBG serum concentrations declined from 71.9 (38.3%) nmole/L at baseline to 58.8 (36%) nmol/L at 3 months after insertion. After that, nearly plateau-like serum concentrations were observed with a tendency to increase towards the end of the observation period.

Table 4. Arithmetic Mean (%CV) of SHBG serum concentration observed after insertion of LCS16 and LCS12 over the 5-year period (N=3) and the 3-year period (N=6 [LCS16], N=7 [LCS12]) in the phase 3 trial (PH-37274).

(nmol/L)	Baseline	C (0.5)	C (3)	C (6)	C (12)	C (18)	C (24)	C (36)
LCS16 (N=6)	96.1 (45.2%)	87.7 (57.3%)	67.1 (50.9%)	63.2 (42.2%)	84.8 (72.4%)	45.6 (47.4%)	54.9 (39.9%)	63.5 (48.6%)
LCS12 (N=7)	71.9 (38.3%)	*59.3 (31.4%)	58.8 (36%)	58.1 (26.5%)	60.0 (25.6%)	47.9 (34.7%)	50.3 (39.1%)	62.4 (30.2%)
	C (42)	**C (48)**	**C(54)**	**C (60)**				
LCS16 (N=3)	#55.1 (57.6%)	44.5 (16.5%)	57.2 (33.9%)	47.0 (30%)				

C (x) = observed concentration at x months after insertion
*n = 6, Subject 160729 had missing data at Month 0.5.
#n = 2, Subject 160702 had missing data at Month 42.

Figure 2. Arithmetic mean concentrations of SHBG (nmol/L) in serum after insertion of LCS16 over the complete study period of 5 years (N=6 for 3 years and N=3 for 5 years) and over 3 years for LCS12 (N=7) in the Phase 3 Efficacy study (PH-37274, large graph: up to 5 years, small graph: first 3 months after insertion)



4.1.2 Population study report: Report R9266

Title: Population pharmacokinetic analysis of levonorgestrel delivered via the intrauterine system LCS16 in female subjects in phase III trial 310442/PH-37274

BACKGROUND

Previously, a population PK model was developed using the Phase 2 study 308901/A46796 and Phase 1 study 92085 (Report No.:A57551) data of LCS12 and it was subsequently refined using the phase 3 trial 310442/A52238 of LCS12 (data up to 3 years of treatment only; Report No: A57552). Both reports were reviewed by Dr. Li Li for the approval of Skyla® (LNG IUS, LCS12, Bayer, NDA 203159) in year 2012 and found to be acceptable from a clinical pharmacology perspective (Dr. Li Li's Clinical Pharmacology review dated 12/05/16 under NDA 203159).

In the current analysis, this previously developed model was applied to the study findings of residual content/serum LNG and SHBG measurements from the 5-year phase 3 trial 310442/ PH-37274.The model was optimized and the impact of two covariates, body weight and age, was tested on the PK of LNG. Subsequently, individual exposure parameters of total and unbound LNG were estimated. Finally, an estimation of the in vivo release rate based on the analysis of residual content of LNG in used IUS was performed.

OBJECTIVES

- Characterize the population PK of LNG in the LCS16 treatment arm from the phase 3 trial 310442/PH-37274, including variability, by applying the population PK model developed in analysis 15904/A57552 to residual content, serum LNG concentration, as well as serum SHBG concentration data from the LCS16 treatment arm from the phase 3 trial 310442/PH-37274.

- Investigate the impact of the covariates body weight and age on the individual LNG exposure.

- Estimate individual total and unbound LNG serum concentrations after 1 month (30 days), 3 months (90 days), 1 year (365 days), 2 years (2x365 days), 3 years (3x365 days), 4 years (4x365 days), 4.5 years (4.5x365 days, rounded to full days) and 5 years (5x365 days): C1m, C3m, C1y, C2y, C3y, C4y, C4:5y and C5y, using the population PK model, as these concentrations cannot be derived directly from the sparsely sampled PK data. The unbound LNG serum concentration was calculated using SHBG and total LNG serum concentrations.

- Estimate in vivo release rates on day 25 (24 days after insertion), after 2 months (60 days after insertion), after 1 year (365 days after insertion), after 3 years (3x365 days after insertion), after 4 years (4x365 days after insertion), after 4.5 years (4.5x365 days after insertion), after 5 years (5x365 days after insertion) and on average (average release rate from insertion until 5 years (5x365 days) after insertion.

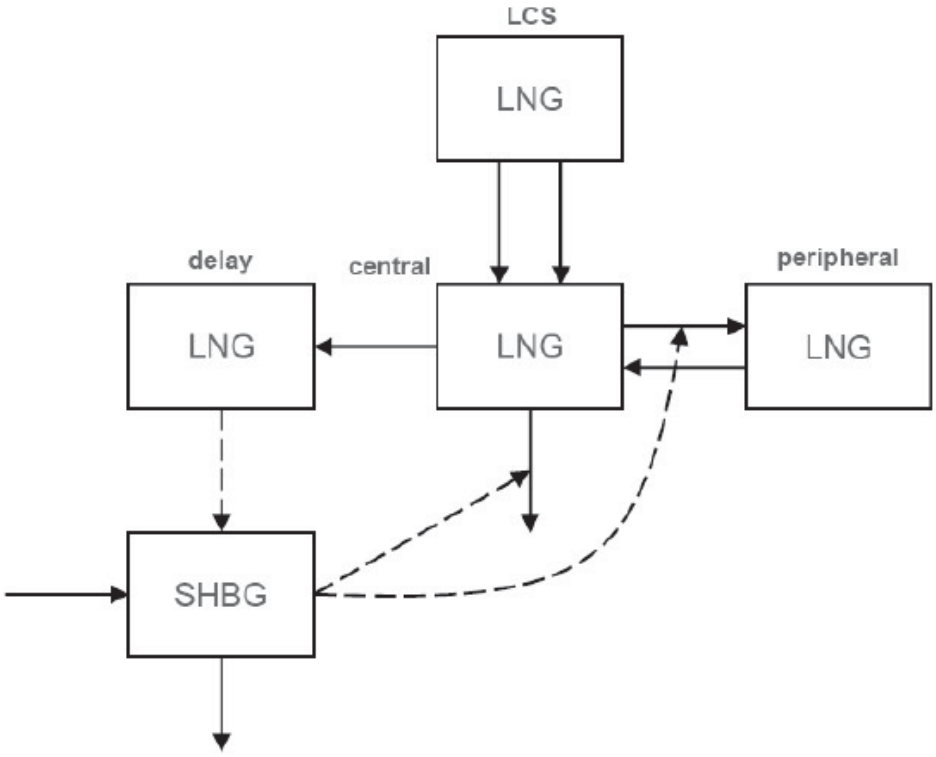
DATA

The dataset contained data from 1329 subjects (1306 included in the analysis) with a total number of 2289 serum LNG concentrations (2253 included in the analysis) and 2436 serum SHBG concentrations (2374 included in the analysis), and 866 measurements of the residual content of LNG in the LCS16 system after removal (854 included in the analysis).

METHODS

The predictive performance of the existing population PK model (O4:run061 from report A57552, model scheme listed in Figure 1, further referred to as existing model) for observations in trial 310042/PH-37274 was tested via a visual predictive check. In addition, this model was applied to all data from trial 310442/PH-37274 with fixed- and random-effects fixed at the original estimates. Subsequently, the performance of the model was evaluated with standard modeling diagnostic tools. In a next step, the existing model was optimized by re-estimating certain model parameters (due to a sparse sampling scheme and because of sufficient amount of prior information, only few parameters were re-estimated.). Model development was geared towards an adequate description of individual exposure in order to acquire reliable Empirical Bayes Estimates of model parameters associated with inter-individual variability (IIV). Once a satisfactory base model with appropriate fixed- and random-effects had been found, the relationship between IIV on the apparent clearance (CL/F) and SHBG baseline (SBL) and the covariates body weight, height, age, BMI, lean body mass and fat mass were explored via a graphical (exploratory) analysis. Potential covariate relationships were further evaluated via a model-based statistical covariate analysis. Using the developed population PK model, individual total and unbound LNG serum concentrations were calculated after 1 month, 3 months, 1 year, 2 years, 3 years, 4 years, 4.5 years and 5 years. Finally, the in vivo release rate of LNG for LCS16 was estimated using the model and residual content data of LNG from time of LCS16 insertion up to 5 years.

Figure 1. Model scheme of the final population PK/PD model LNG/SHBG for both LCS treatments LCS12 and LCS16 from analysis A57552 (Source: Figure 6.2.1 of Report R-9266)



For the release from the LCS two release processes are assumed (one release through the membrane and the other one through the open ends of the device). A two-compartment model to describe the PK of LNG is chosen. SHBG has an influence on the PK of LNG since only the unbound LNG is cleared. The effect of LNG on SHBG is modeled by introduction of a delay compartment. The production and elimination of SHBG is descr bed by a one-compartment model. Solid lines denote a mass flow, dashed lines indicate an indirect influence.

RESULTS

- **Population PK model optimization**
  The previously developed population PK model which was then optimized in the present analysis (final model) provides an adequate description of LNG and SHBG serum concentrations and residual content data from trial 310442/PH-37274 after insertion of LCS16 in all subjects with at least one valid PK measurement (LNG or SHBG serum concentration above the LLOQ or a residual content measure).

  The final population PK model consists of the following components:
  - The LNG release from the LCS system e into the central compartment, representing the serum LNG concentration here, is described by a combination of a zero-order release and a time-dependent first-order release.
  - The biphasic LNG disposition in the serum is described by a two-compartment model with LNG binding to albumin (here assumed to be constant) and to SHBG in serum. It is assumed that from serum only unbound LNG can be eliminated and distributed to peripheral tissue.
  - The change in endogenous SHBG in serum over time is described using a one-compartment model assuming a constant, zero-order, endogenous SHBG synthesis rate, and a first-order elimination rate. It is assumed that the SHBG synthesis is inhibited by LNG where the effect of the LNG concentration on the SHBG synthesis rate is linear and delayed.
  - Inter-individual variability was identified on the apparent clearance (CL/F) of LNG and on the parameter for the SHBG serum concentration at baseline (SBL) with covariance between the two terms.

- **Covariate analysis**
  The correlation between body weight and CL/F that was identified in the previous analysis is also valid for the present analysis. CL/F of LNG increases linearly with 0.84% per kg body weight for the body weight range within trial 310442/PH-37274 (39 to 160 kg, median 65 kg with corresponding CL/F values of 188-432 L/h for the range and 240 L/h for the median, respectively). Age does not have a significant effect on the PK of LNG in trial 310442/PH-37274.

- **Calculation of individual concentrations**
  Based on the final model, total and unbound LNG concentrations were estimated for all subjects. The summary statistics of the total and unbound LNG concentrations for the complete study population are listed in Table 1 and Table 2. The mean serum concentrations of total LNG decrease slowly from average concentrations (%CV) at 1 month of 164 (39.1%) ng/L to average concentrations at 5 years of 89.7 (39.3%) ng/L. The predicted mean of unbound LNG decreases from 2.42 (24.5%) ng/L at 1 month to 1.27 (24%) ng/L at 5 years of treatment (only about 1.5% of total LNG is unbound).

Table 1. Summary statistics of **total** LNG serum concentration estimated based on the population PK model for the complete LCS16 study population at pre-defined time points (Source: Table 7.3:6 of Report R-9266)

	1 month	3 months	1 year	2 years	3 years	4 years	4.5 years	5 years
N	1253	1223	1109	963	774	666	624	224
Arithmetic mean	164	153	125	108	98.9	93.5	91.6	89.7
LL 95% CI[a]	160	150	122	105	96.1	90.5	88.6	85.0
UL 95% CI[b]	168	157	128	111	102	96.5	94.6	94.3
Arithmetic SD[c]	64.2	60.5	50.3	43.9	40.9	39.4	38.3	35.2
Arithmetic CV[d]	39.1	39.4	40.3	40.7	41.3	42.1	41.8	39.3
Geometric mean	152	142	115	99.7	91.3	86.2	84.5	83.1
LL 95% CI[a]	149	139	113	97.3	88.8	83.6	81.9	78.9
UL 95% CI[b]	156	146	118	102	94.0	88.9	87.2	87.5
Geometric SD[d]	1.47	1.47	1.48	1.49	1.49	1.50	1.49	1.48
Geometric CV[c]	40.1	40.3	41.0	41.2	41.7	42.3	41.8	41.1
Median	154	145	118	101	93.3	88.0	86.2	83.7
LL 95% CI[a]	150	142	115	98.5	90.3	84.9	83.1	78.8
UL 95% CI[b]	158	149	121	104	96.4	91.1	89.3	88.6
Minimum	52.7	48.9	39.2	33.4	30.4	28.6	28.0	27.4
5th percentile	78.1	72.7	58.6	50.6	46.5	43.4	44.3	44.5
95th percentile	281	262	215	186	170	164	157	153
Maximum	513	486	412	364	338	322	316	206

[a]lower limit of the 95% confidence interval
[b]upper limit of the 95% confidence interval
[c]standard deviation
[d]coefficient of variation (%)

Table 2. Summary statistics of **unbound** LNG serum concentration estimated based on the population PK model for the complete LCS16 study population at pre-defined time points (Source: Table 7.3:7 of Report R-9266)

	1 month	3 months	1 year	2 years	3 years	4 years	4.5 years	5 years
N	1253	1223	1109	963	774	666	624	224
Arithmetic mean	2.42	2.25	1.80	1.54	1.40	1.32	1.29	1.27
LL 95% CI[a]	2.39	2.22	1.77	1.52	1.38	1.30	1.27	1.23
UL 95% CI[b]	2.45	2.28	1.83	1.56	1.43	1.35	1.32	1.31
Arithmetic SD[c]	0.592	0.551	0.439	0.373	0.343	0.326	0.316	0.304
Arithmetic CV[d]	24.5	24.5	24.4	24.3	24.5	24.7	24.5	24.0
Geometric mean	2.35	2.18	1.75	1.49	1.36	1.28	1.25	1.23
LL 95% CI[a]	2.31	2.15	1.72	1.47	1.34	1.26	1.23	1.19
UL 95% CI[b]	2.38	2.21	1.77	1.52	1.38	1.30	1.28	1.27
Geometric SD[d]	1.29	1.29	1.29	1.29	1.29	1.29	1.29	1.29
Geometric CV[c]	25.8	25.7	25.6	25.5	25.6	25.9	25.6	25.5
Median	2.39	2.23	1.78	1.52	1.39	1.31	1.28	1.26
LL 95% CI[a]	2.36	2.19	1.75	1.49	1.36	1.28	1.25	1.22
UL 95% CI[b]	2.43	2.26	1.81	1.55	1.41	1.33	1.31	1.31
Minimum	1.10	1.02	0.811	0.690	0.628	0.591	0.596	0.585
5th percentile	1.48	1.38	1.13	0.964	0.879	0.816	0.815	0.804
95th percentile	3.43	3.19	2.55	2.17	1.98	1.88	1.83	1.78
Maximum	4.55	4.22	3.26	2.77	2.53	2.38	2.32	2.14

[a]lower limit of the 95% confidence interval
[b]upper limit of the 95% confidence interval
[c]standard deviation
[d]coefficient of variation (%)

- **Determination of *in vivo* LNG release rate**
  The model used for the determination of *in vivo* LNG release rate was identical to the approach for the release process used in the population PK analysis. The developed release model in the population PK model, i.e., the combination of a zero-order release and a time-dependent first-order release, was fitted to the residual content data only to estimate *in vivo* release rates. All the in vivo release rates are listed in Table 3. Based on the population PK approach, the in vivo release rate of LCS16 was 17.5 µg/day at day 25 and declined to 9.79 µg /day at 1 year and 7.89 µg/day at 3 years after insertion. Thereafter, the release rate remained relatively stable until the end of year 5 (7.44 µg/day). The calculated average release rate over the entire time of LCS16 use was about 9 µg/day.

  Table 3. Model-based estimated in vivo release rates from LCS16 (Source: Table 7.4:8 of Report R-9266)

Time point	Days after insertion	In vivo release rates (µg/day)
Day 25	24	17.5
2 months	60	15.3
1 year	365	9.79
3 years	1095	7.89
4 years	1460	7.61
4.5 years	1643	7.52
5 years	1825	7.44
Mean over 5 years	1825	8.99

Reviewer's Comments:
The sponsor's analyses appear to be reasonable.

4.2 Cover Sheet OCPB Filing/Review Form

CLINICAL PHARMACOLOGY FILING FORM

Application Information

NDA Number	208224	**SDN**	1
Applicant	Bayer HealthCare Pharmaceuticals, Inc.	**Submission Date**	November 18, 2015
Generic Name	Levonorgestrel-releasing intrauterine system (LCS16)	**Brand Name**	Kyleena
Drug Class	Hormonal contraceptive		
Indication	Prevention of pregnancy for up to 5 years		
Dosage Regimen	Intrauterine system containing (b) (4) mg of levonorgestrel with an initial release rate of (b) (4) µg/day		
Dosage Form	Intrauterine system	**Route of Administration**	Intrauterine
OCP Division	DCP3	**OND Division**	DBRUP
OCP Review Team	**Primary Reviewer(s)**	**Secondary Reviewer/ Team Leader**	
Division	Li Li (CDER)	Myong Jin Kim	
Pharmacometrics	N/A	N/A	
Genomics	N/A	N/A	
Review Classification	☑ Standard ☐ Priority ☐ Expedited		
Filing Date	1/17/2016	**74-Day Letter Date**	1/31/2016
Review Due Date	7/18/2016	**PDUFA Goal Date**	9/18/2016

Application Fileability

Is the Clinical Pharmacology section of the application fileable?

☑ Yes

☐ No

If no list reason(s)

Are there any potential review issues/ comments to be forwarded to the Applicant in the 74-day letter?

☑ Yes

☐ No

Is there a need for clinical trial(s) inspection?

☐ Yes

☑ No

If yes explain

Clinical Pharmacology Package

Tabular Listing of All Human Studies	☑ Yes ☐ No	Clinical Pharmacology Summary	☑ Yes ☐ No
Bioanalytical and Analytical Methods	☑ Yes ☐ No	Labeling	☑ Yes ☐ No

Clinical Pharmacology Studies

Study Type	Count	Comment(s)
In Vitro Studies		
☐ Metabolism Characterization		
☐ Transporter Characterization		
☐ Distribution		

☐ Drug-Drug Interaction			
In Vivo Studies			
Biopharmaceutics			
☐ Absolute Bioavailability			
☐ Relative Bioavailability			
☐ Bioequivalence			
☐ Food Effect			
☐ Other			
Human Pharmacokinetics			
Healthy Subjects	☐ Single Dose		
	☐ Multiple Dose		
Patients	☐ Single Dose		
	☐ Multiple Dose		
☐ Mass Balance Study			
☐ Other (e.g. dose proportionality)			
Intrinsic Factors			
☑ Race		1	
☐ Sex			
☐ Geriatrics			
☑ Pediatrics		1	
☐ Hepatic Impairment			
☐ Renal Impairment			
☐ Genetics			
Extrinsic Factors			
☐ Effects on Primary Drug			
☐ Effects of Primary Drug			
Pharmacodynamics			
☐ Healthy Subjects			
☐ Patients			
Pharmacokinetics/Pharmacodynamics			
☐ Healthy Subjects			
☑ Patients		2	
☐ QT			
Pharmacometrics			
☑ Population Pharmacokinetics		5	
☐ Exposure-Efficacy			
☐ Exposure-Safety			

Total Number of Studies	**In Vitro**		**In Vivo**	9
Total Number of Studies to be Reviewed				9

Criteria for Refusal to File (RTF)		
RTF Parameter	**Assessment**	**Comments**
1. Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	☐Yes ☐No ☑N/A	
2. Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)	☑Yes ☐No ☐N/A	
3. Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?	☐Yes ☐No ☐N/A	
4. Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application?	☐Yes ☐No ☑N/A	505 (b)(1)
5. Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?	☑Yes ☐No ☐N/A	
6. Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?	☐Yes ☐No ☐N/A	
7. Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for each primary study that supports items 1 to 6 above (in .xpt format if data are submitted electronically)?	☑Yes ☐No ☐N/A	
8. Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)?	☑Yes ☐No ☐N/A	
9. Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a manner to allow substantive review to begin? If provided as an electronic submission, is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work leading to appropriate sections, reports, and appendices?	☑Yes ☐No ☐N/A	
Complete Application **10.** Did the applicant submit studies including study reports, analysis datasets, source code, input files and key analysis output, or justification for not conducting studies, as agreed to at the pre-NDA or pre-BLA meeting? If the answer is 'No', has the sponsor submitted a justification that was previously agreed to before the NDA submission?	☑Yes ☐No ☐N/A	

Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality) Checklist		
Data		
1. Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	☑Yes ☐No ☐N/A	
2. If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	☐Yes ☐No ☑N/A	
Studies and Analysis		
3. Is the appropriate pharmacokinetic information submitted?	☑Yes ☐No ☐N/A	
4. Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	☑Yes ☐No ☐N/A	
5. Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	☑Yes ☐No ☐N/A	
6. Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	☑Yes ☐No ☐N/A	
7. Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?	☐Yes ☐No ☑N/A	
General		
8. Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	☑Yes ☐No ☐N/A	
9. Was the translation (of study reports or other study information) from another language needed and provided in this submission?	☐Yes ☐No ☑N/A	

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

/s/

LIN ZHOU
08/19/2016

MYONG JIN KIM
08/19/2016