CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203159Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW ADDENDUM

NDA 203159	Submission Date(s)	12/09/2011, 07/02/2012, 07/17/2012, 07/25/2012. 11/09/2012, 12/10/2012
Brand Name	Skyla	
Generic Name	levonorgestrel-releasing intrauterine system (LCS12)	
Reviewer	Li Li, PhD	
Acting Team Leader	Myong Jin Kim, PharmD	
OCP Division	Division of Clinical Pharmacology 3	
OND Division	Division of Reproductive and Urologic Products	
Sponsor	Bayer HealthCare Pharmaceuticals Inc	
Submission Type	Original	
Formulation; Strengths; Regimen	Intrauterine system containing 13.5 mg of levonorgestrel with an initial release rate of (b) (4) µg/day	
Proposed Indication	Prevention of pregnancy for up to 3 years	

1 Executive Summary

The Clinical Pharmacology review of NDA 203159 (DARRTS, December 5, 2012) stated that NDA 203159 was acceptable provided that an agreement is reached between the sponsor and the Division regarding the language in the package insert labeling. The final agreement was reached on January 7, 2013 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 NDA 203159 acceptable.

5 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

LI LI
01/07/2013

MYONG JIN KIM
01/07/2013
I concur.

Clinical Pharmacology Review	
NDA Number:	203159
Submission Dates:	12/09/2011, 07/02/2012, 07/17/2012, 07/25/2012
Brand Name:	Skyla™
Generic Name:	levonorgestrel-releasing intrauterine system (LCS12)
OCP Reviewer:	Li Li, Ph.D
OCP Team Leader:	Myong Jin Kim, Pharm. D
PBPK modeling Reviewer	Ping Zhao, Ph.D
OCP Division:	Division of Clinical Pharmacology III
OND Division:	Division of Reproductive and Urologic Products
Sponsor:	Bayer HealthCare Pharmaceuticals Inc.
Submission Type:	Original
Formulation and Dosing regimen:	Intrauterine system containing 13.5 mg of levonorgestrel with an initial release rate of (b) (4) µg/day
Indication:	Prevention of pregnancy for up to 3 years

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Executive Summary

Reference ID: 3226051

The Sponsor submitted a New Drug Application (NDA) for LCS12, a levonorgestrel (LNG) intrauterine system (IUS), for the indication of prevention of pregnancy for up to 3 years on December 9, 2011. Worldwide, there is no marketing authorization for LCS12. Mirena®, the only LNG-IUS currently on the market, was approved in the U.S. on December 6, 2000 under NDA 021225. In comparison to Mirena®, LCS12 has a smaller T-frame, a lower daily release rate of LNG, and a shorter duration of use (up to 3 years rather than 5 years). A silver ring is added around the vertical stem of the T-frame to facilitate detection during ultrasound examination. Additionally, the insertion tube diameter for LCS12 is smaller than that of Mirena®, which may result in an easier and less painful insertion procedure, particularly in young and nulliparous women.

In support of this NDA, the Sponsor conducted a pivotal Phase 3 study (A52238) and a supporting Phase 2 study (A46796) evaluating contraceptive efficacy, bleeding patterns, as well as safety parameters. No specific clinical pharmacology study was conducted with LCS12. The pharmacokinetic (PK) and pharmacodynamic (PD) characterization of LCS12 were mainly based on the Phase 2 and Phase 3 studies. Specifically, the PK parameters of LCS12 were determined by non-compartmental analysis via a dense sampling scheme in a subset of 12 women in both clinical studies, and by a population PK analysis via a sparse sampling scheme in the Phase 3 study (A57551 and A57552). The PD characteristics including effects on ovulation, cervix, endometrium and serum silver concentrations were investigated in a subset of 20 women per treatment arm in both clinical studies. Additional supporting data include a Physiology-based PK (PBPK) analysis comparing the PK of LNG between female adolescents (10-18 years old) and adults following LCS12 insertion (A57120), one *in vitro* study determining LNG protein binding (A36505) and one *in vitro* study identifying cytochrome P450 (CYP) isoenzymes involved in LNG metabolism (A02495). In addition, the Sponsor also submitted two *in vivo* supplementary studies, i.e., Study A229 characterizing the PK of LNG following intravenous (i.v.) and oral administration, and Study A10982 describing the course of LNG concentrations at early times after Mirena® insertion and after Mirena® removal.

Out of the 7 study reports submitted under the clinical pharmacology section, 5 containing relevant information acquired during LCS12 development were reviewed, the two not reviewed are supplementary studies (A229 and A10982) conducted with different formulations or dosing regimen. PK characterization of LCS12 using the Phase 2 data was not reviewed given the change in formulation in the Phase 3 study. In addition, PD characterization of LCS12 was reviewed by the clinical reviewer.

1.1 Recommendations

The Office of Clinical Pharmacology/ Division of Clinical Pharmacology 3 (OCP/DCP3) finds NDA 203159 acceptable provided that agreement is reached between the Sponsor and the Division regarding the language in the package insert.

1.2 Phase IV Requirement

None

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

<u>*In vivo* release rate</u>

Release of LNG from the LCS12 starts immediately after placement in the uterine cavity. The release rate is approximately 14 µg/day after 24 days and reduces to 10 µg/day after 60 days and then decreases progressively to 5 µg/day after 3 years. The average delivery rate of LNG is approximately 6 µg/day over a period of 3 years.

<u>Absorption, Distribution, Metabolism, and Excretion (ADME)</u>

- Absorption

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Non-compartmental analysis using data from subset population in the Phase 3 study (N=7) indicated that the maximum serum concentration (C_{max}) of LNG was 192 ± 105 ng/L, reached after 2 days of LCS12 insertion (median). Thereafter, LNG serum concentration of decreased slowly to the mean value (C_{ave}) of 75 ± 32 ng/L. 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 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 slightly during the first 1 to 2 weeks after insertion. Thereafter, nearly plateau-like serum concentrations were observed with a tendency to increase towards the end of the study after 3 years of treatment.

- Metabolism
  LNG is almost completely metabolized. No pharmacologically active metabolites of LNG have been identified. Most of the metabolites that circulate in the blood are sulfates of 3α, 5β-tetrahydro-LNG, while excretion occurs predominantly in the form of glucuronides. Data from i*n vitro* study demonstrated that oxidative metabolism of LNG was catalyzed by CYP enzymes, especially CYP3A4.

- Excretion:
  Following i.v. administration of 0.09 mg LNG to healthy volunteers, the total clearance of LNG from plasma is approximately 1 mL/min/kg and the elimination half-life is approximately 20 hours. Only trace amounts of LNG are excreted in unchanged form. The metabolites are excreted with feces and urine at an excretion ratio of about 1.

Drug Product Formulation

Phase 2 Formulation vs Phase 3 Formulation

The formulations of LCS12 used in the Phase 2 and Phase 3 clinical studies were slightly different. (b) (4) Other changes were the addition of a silver profile (ring) and some modifications in the design of the T-body. Given that the safety and efficacy of LCS12 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

Compared to the Phase 3 formulation, minor modifications have been implemented for the TBM product, namely, the removal threads, the modified inserter and further minor modifications of the T-body. The clinical and TBM formulations of LCS12 are presented in **Table 4**. Per Biopharmaceutics reviewer Dr. Sandra Suarez Sharp, based on the level of changes in the TBM product, a bridging study is needed and the bridging for the formulation change can be supported by *in vitro* dissolution data. The Sponsor submitted the requested bridging data on May 17, 2012, claiming that the f2 test indicated the similarity between Phase 3 and TBM formulation. Dr. Sandra Suarez Sharp agreed with the conclusion.

Drug-Drug Interactions (DDI):

No clinical DDI study was conducted under this NDA. Information from *in vitro* DDI studies conducted with LNG in the current NDA submission is presented below:

Effects of Other Drugs on LNG

Reference ID: 3226051

In vitro studies (A02495) demonstrated that LNG was mainly metabolized by CYP3A4. Thus, drugs affecting the activity of CYP3A4 may change the PK of LNG.

Effects of LNG on other Drugs

In vitro studies (A02495) indicated the inhibitory effect of LNG on CYP3A4 activity. However, LNG is unlikely to affect the metabolism of other drugs by CYP3A4, because C_{max} value of LNG from LCS12 was about four orders of magnitude lower than the determined IC_{50} value. In addition, LNG did not affect the metabolism of the other model substrates of CYP1A2, 2A6, 2C9, 2C19, 2D6 and 2E1 *in vitro*.

Specific Populations:

Renal / hepatic impairment:

No formal studies have evaluated the effect of renal or hepatic disease on the disposition of LCS12.

Due to mainly local action of LCS12, the efficacy would not be compromised. Serum concentration of LNG could be elevated in women with impaired renal or hepatic function. However, considering the dose of LNG in LCS12 is about 10 times lower than that in LNG-containing oral contraceptives, no critical concentrations are expected during the use of LCS12 in women with renal or hepatic impairment.

Pediatric study:

Pre-menarche children:

The Sponsor has requested a partial waiver for pre-menarche children as they are not at risk of becoming pregnant.

Post-menarcheal adolescents:

The Sponsor requested that the Pediatric Research Equity Act (PREA) requirements for postmenarcheal pediatric patients be deemed fulfilled by extrapolation of adult data. The Sponsor plans to conduct a multi-center, single-arm study to assess the safety, efficacy, discontinuation rate and PK of LCS12 (b) (4) [redacted] The Division will request the Sponsor submit the data once the study is completed in Europe.

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.

LNG serum concentration: radioimmunoassay (RIA) based on the specific antiserum preparation and tritium labeled LNG

SHBG serum concentration: time-resolved fluoroimmunoassay (TR-FIA)

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2 QUESTION BASED REVIEW

2.1 GENERAL ATTRIBUTES

2.1.1 What is LCS12 and what is the difference between LCS12 and Mirena®?

LCS12 (Skyla™) is a levonorgestrel (LNG) intrauterine system (IUS) indicated for the prevention of pregnancy for up to 3 years. The initial (in weeks 3 to 4) *in vitro* release rate of LCS12 is approximately 12 µg/day.

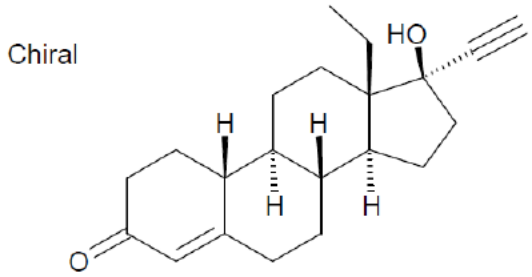
Mirena® is the only LNG-IUS currently approved for the prevention of pregnancy in the U.S. with an initial *in vitro* release rate of 20 µg/day. In comparison with Mirena®, LCS12 has a smaller T-frame, a lower daily release rate of LNG, and a shorter duration of use (up to 3 years rather than 5 years). A silver ring is added around the vertical stem of the T-frame to facilitate detection during ultrasound examination. Additionally, the insertion tube diameter for LCS12 is smaller than that of Mirena® which may result in an easier and less painful insertion procedure, particularly in young and nulliparous women.

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 LCS12 is LNG. LNG USP is a white to off-white crystalline powder chemically described as (-)-13-Ethyl-17-hydroxy-18, 19-dinor-17 alpha-pregn-4-en-20-yn-3-one. The structural formula is presented in **Figure 1**.

Figure 1 LNG chemical structure



$C_{21}H_{28}O_2$ MW 312.45

Formulation:

As shown in **Figure 2**, LCS12 consists of a hormone-elastomer reservoir mounted on a T-shaped polyethylene frame (T-body). The drug reservoir is composed of a mixture of 13.5 mg LNG (b) (4) and polydimethylsiloxane (PDMS) membrane which covers the reservoir (b) (4) The T-body has a loop at one end of the vertical stem and two horizontal arms at the other end. Detection and differentiation of the LCS12 T-body by ultrasound is facilitated by the addition of a silver ring in the upper part of the vertical stem in the T-body. Other excipients in LCS12 include silica colloidal anhydrous (SiO2; silicon dioxide, colloidal) and barium sulfate.

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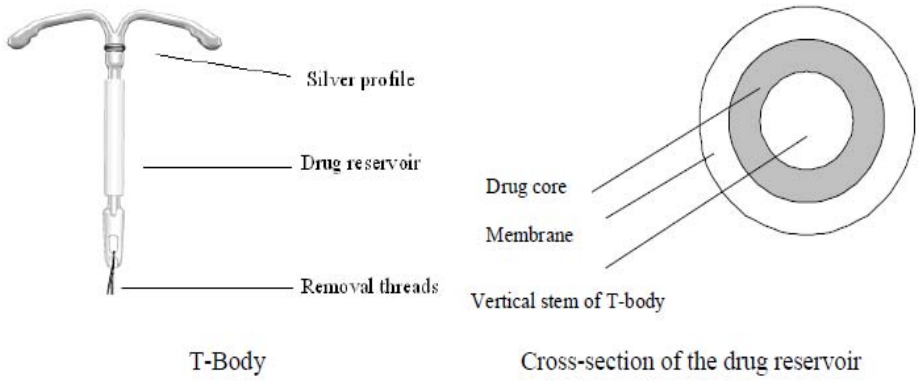
Figure 2 Schematic illustration of LCS12 and a cross-section of the drug reservoir



2.1.3 What is the proposed mechanism of action?

The contraceptive effect of LCS12 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.

2.1.4 What are the clinical and clinical pharmacology data submitted to support the approval of LCS12?

Clinical Studies

In support of this NDA, the Sponsor conducted a pivotal Phase 3 study (A52238) and a supporting Phase 2 clinical study (A46796) evaluating contraceptive efficacy, bleeding patterns, as well as safety parameters.

- Phase 2 Study (A46796): It was a dose-finding study investigating LCS12 and LCS16 compared with Mirena® for a maximum of 3 years. LCS16 is a LNG IUS with an initial *in vitro* release rate of 16 μg/day. The results from this study indicated that both investigational doses demonstrated similar efficacy and safety, and thus LCS12 would be considered as the lowest safe and effective dose over a 3-year period of treatment. This study was conducted outside of the U.S.
- Phase 3 Study (A52238): It was a pivotal safety and efficacy study evaluating LCS12 and LCS16 for 3-year period of treatment. The investigation on LCS16 is extended for additional 2 years to explore its potential as a 5-year product. In the study, a total of 1432 women of 18 to 35 years old were assigned for LCS12 assessment. The mean body mass index (BMI) was 25.32 kg/m^2 with 17% of study subjects having a BMI over 30 kg/m^2. This study was conducted in the U.S. under IND 073505.

Clinical Pharmacology Studies:

No dedicated clinical pharmacology studies were conducted with LCS12.

- PK Characterization:
  The PK characterization of LCS12 was mainly based on the Phase 2 and Phase 3 studies. In both studies, a dense sampling scheme was conducted in a subset of 12 women to determine non-compartmental PK parameters of LNG during LCS12 treatment. In the Phase 3 study, a sparse sampling scheme (one sample/subject) was conducted in all subjects for a population PK analysis (A57551, A57552).
- PD Characterization:
  The PD characteristics including effects on ovulation, cervix, and endometrium, as well as evaluation of serum silver concentrations released from the silver ring on the T-body of LCS12 were investigated in a subset of 20 women per treatment arm in both clinical studies. Additional

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Supporting Data

- A Physiology-based PK (PBPK) analysis comparing the PK of LNG between female adolescents (10-18 years old) and adults following LCS12 insertion (A57120)
- *In vitro* study determining LNG protein binding (A36505)
- *In vitro* study identifying cytochrome P450 (CYP) isoenzymes involved in LNG metabolism (A02495)
- Two *in vivo* supplementary studies, i.e., Study A229 characterizing the PK of LNG following intravenous (i.v.) and oral administration, and Study A10982 describing the course of LNG concentrations at early times after Mirena® insertion and after Mirena® removal.

The detailed information for submitted clinical pharmacology studies is summarized in **Table 1**.

Table 1 Summary of Clinical Pharmacology Studies

Study No.	**Study Design/Description**	**Main objectives regarding to PK/PD parameters**
A46796 (Phase 2, Europe)	Multicenter, randomized, open, controlled, 3-arm (LCS12, LCS16, and Mirena®), parallel group for 3 years	• PD - Ovarian, cervical function and hormone concentrations (N = 20/arm) - endometrial histology (N = 30/arm) • PK of LNG and SHBG (N = 12/ arm)
A52238 (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 = 20/arm - endometrial histology (N = 30/arm) • PK of LNG and SHBG, Serum silver ion concentration (N = 12/ arm)
A57551	Development of population PK model	Development of a population PK model based on phase 2 data for the description of LNG PK in serum
A57552	Population PK Evaluation of Phase 3	• Application of the developed population PK model • Estimation of LNG serum concentrations over the 3 years of use of LCS12 • Investigations on the impact of body weight and other covariates
A57120	PBPK study – Pediatric Scaling	Development of a physiologically based PK model to predict the PK of LNG in adolescents after application of LCS
A36505	Calculation of LNG protein binding according to a mathematical model	LNG protein binding (model) to predict free fraction of LNG
A02495	*In vitro* study: drug interaction and metabolism study	• CYP isozymes involved in LNG metabolism and enzyme kinetics of LNG • Inhibitory effect of LNG on metabolism of CYP Isozymes
A229	Single center, randomized, open, single dose, cross-over	• PK parameters (i.v. treatment) • dose linearity of the oral drug product
A10982	Multicenter, open, non-randomized for 1 year	PK of LNG after Mirena® insertion and removal

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2.2 GENERAL CLINICAL PHARMACOLOGY

2.2.1 Is the proposed dose and dosing regimen acceptable?

Yes. In the clinical development of this product, the Sponsor conducted a Phase 2 dose-finding study (A46796) investigating the contraceptive efficacy and safety of LCS12 and LCS16 compared with Mirena® for a maximum of 3 years. The results of this study indicated that both investigational doses demonstrated similar efficacy and safety, and thus LCS12 was considered as the lowest safe and effective dose over a 3-year period of treatment. LCS16 is currently being evaluated as an IUS for a 5-year of use.

2.2.2 What is the release rate of LNG from LCS12?

The *in vivo* release rates of LNG based on *ex vivo* residual content data in Phase 3 study (A52238) was calculated using NONMEM. The release rate is approximately 14 µg/day after 24 days and reduces to 10 µg/day after 60 days and then decreases progressively to 5 µg/day after 3 years. The average delivery rate of LNG is approximately 6 µg/day over a period of 3 years.

The Sponsor also established an IVIVC model. (b) (4) Per Biopharmaceutics reviewer Dr. Sandra Suarez Sharp, the proposed IVIVC model failed to adequately predict the LNG *in vivo* release for the first three months after insertion.

(b) (4) . Consequently, the initial LNG *in vitro* release of LCS12 on Day 2 (b) (4) is slightly higher than that measured for Mirena® of around (b) (4) and declines to a value of about (b) (4) for the sampling period of Days 19-25 which is about half the value obtained for Mirena® around that time. The "burst" effect of LCS12 (b) (4) may not compromise the contraceptive efficacy, nor may lead to critical systemic exposure. However, the potential effect of high local concentration due to an initial burst release on the uterus is not known.

2.2.3 What are the PK characteristics of LCS12

No dedicated PK study was conducted for LCS12. The PK characterization of LCS12 was mainly based on the PK components in the clinical studies. Given the formulation changes from Phase 2 to Phase 3 studies, only PK data in the pivotal Phase 3 study (A52238) were reviewed.

Based on the data from Phase 3 study, the PK of LCS12 was characterized using the following:

- Non-compartmental analysis: a dense sampling scheme in a subset group of 12 subjects
- Population PK analysis: a sparse sampling scheme at one sample per subject

<u>Non-compartmental analysis</u>

- Study Design:

A subset of 12 subjects were enrolled to characterize the PK of LCS12. During the 3 years of LCS12 treatment, serum concentration of LNG were measured at day 1, 3, 7 and 14 after start of treatment and thereafter at every regular visit (3, 6, 9, 12, 18, 24, 30, and 36 month).

- Study Results:

After insertion of LCS12, an arithmetic mean of maximum serum concentration (C_{max}) of LNG was 192 ± 105 ng/L, reached after 2 days (median). Thereafter, the serum concentration of LNG decreased slowly to the mean value (C_{ave}) of 75 ± 32 ng/L. The PK profile of LNG after LCS12 insertion is presented in **Figure 3** with PK parameters summarized in **Table 2.**

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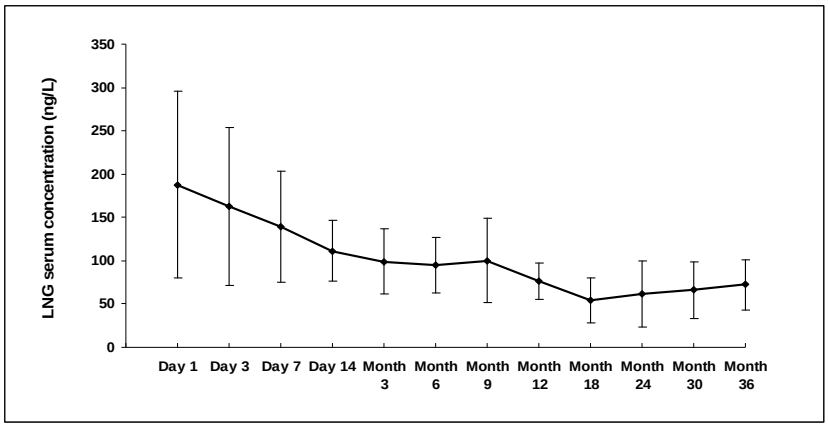
Table 2 Arithmetic Mean (SD) PK parameters of LNG observed after insertion of LCS12 (N=7*)

$AUC_{(0\text{-}tlast)}$ (ng·d/L)	C_{max} (ng/L)	t_{max} (d)	C_{ave} (ng/L)	C_{min} (ng/L)	t_{min} (d)	C_{last} (ng/L)	t_{last} (d)
82083 (34674)	192 (105)	2.00 (1.00-16.0)	75 (32)	48 (30)	733 (546-1085)	72 (29)	1085 (1083-1135)

- For all PK parameters the arithmetic means with the standard deviation (SD, in parentheses) are given, except for tmax, tmin and tlast, where the median and the range (in parentheses) are provided.
- AUC(0-tlast) = area under the drug concentration vs time curve from time 0 to the last data point >LLOQ
- Cav = average steady state concentration (AUC(0-tlast)/ tlast)
- * Data from 7 subjects are used for LCS12 PK analysis. The subjects not eligible for PK analysis either did not have 3- year LNG and SHBG samples or had more than one missing sample around tmax.
- * includes 2 subjects each with one concentration value < LLOQ (Subjects160734 and160753) which were set to ½ LLOQ for evaluation.

Figure 3 Arithmetic mean (±SD) LNG concentrations-Time profile following insertion of LCS12 (N=7)



Population PK analysis

- Model Establishment

The population PK/PD model was initially developed based on the Phase 2 study (A308901). As shown in **Figure 4**, two release processes (b) (4) were used to describe the release of LNG from LCS12. A two-compartment model to describe the PK of LNG was chosen. SHBG had an influence on the PK of LNG since only the unbound LNG was cleared. The effect of LNG on SHBG was modeled by introduction of a delay compartment. The production and elimination of SHBG were described by a one-compartment model. Later on, the established PK/PD model was applied to data from the Phase 3 study (A52238). The data were well described by the model, but optimization of the release parameters was nevertheless necessary given the formulation changes between the Phase 2 and Phase 3 study (details of model validation can be found in the individual study review).

Figure 4 Model scheme of the final population PK/PD model LNG/SHBG for LCS12. Solid lines denote a mass flow; dashed lines indicate an indirect influence.

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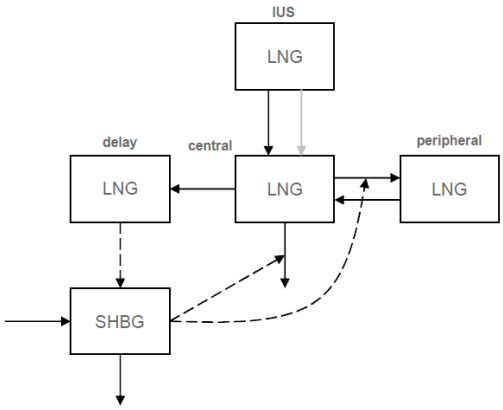

- Model Prediction

Based on this model, individual total and unbound LNG serum concentrations after 1 day, 7 days, 30 days, 3 months, 1 year, 2 years and 3 years were estimated for the entire study population. The geometric mean concentration values of total LNG for LCS12 at different time points after insertion are summarized in **Table 3**.

Table 3: Estimated geometric means of total LNG concentrations (ng/L) at different time points after insertion of LCS12

	1 day	7 days	30 days	3 months	1 year	2 years	3 years
Subject numbers (N)	1222	1222	1209	1176	1061	913	723
LNG concentration	116	162	131	99.8	71.0	64.3	58.6
Geometric CV (%)	18.1	27.5	26.8	27.2	27.3	27.6	29.4
Median	117	165	133	101	71.8	64.7	58.5
Minimum	65.9	71.9	58.8	44.5	31.6	28.4	30.9
5th percentile	85.8	102	83.0	62.8	44.4	40.6	36.2
95th percentile	154	249	198	153	109	99.5	91.9
Maximum	221	424	325	256	188	171	164

The population PK analysis was found to be reasonable with the data well described by the final model.

2.2.4 What are the ADME characteristics of LNG released from LCS12

The absorption of LNG after release from LCS12 is described in Section **2.2.2**.

- 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 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 slightly during the first 1 to 2 weeks after insertion. Thereafter, nearly plateau-like serum concentrations were observed with a tendency to increase towards the end of the observation period. The serum concentrations of SHBG after insertion of LCS12 are presented in **Figure 5** and **Table 4**.

Figure 5: Arithmetic mean (±SD) SHBG concentrations-Time profile following insertion of LCS12

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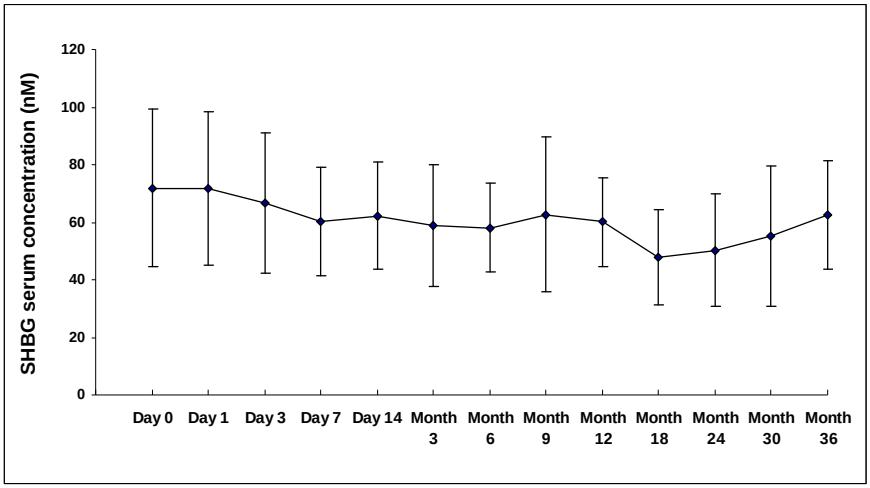
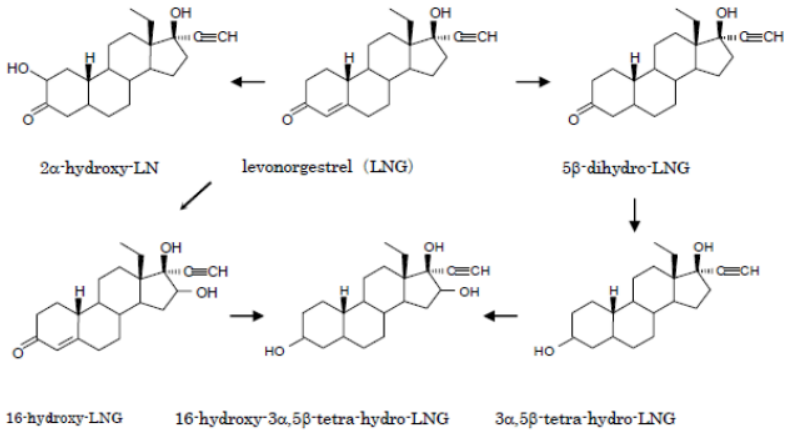


Table 4 Arithmetic mean (SD) concentrations of SHBG (nmol/L) in serum after insertion of LCS12

	Baseline	**C (0.5 month)**	**C (3 month)**	**C(6 month)**	**C(12 month)**	**C(18 month)**	**C(24 month)**	**C(36 month)**
Mean (nM)	72	59	59	58	60	48	50	62
SD	28	18	21	15	15	17	20	19

- **Metabolism**
  LNG is almost completely metabolized. No pharmacologically active metabolites of LNG have been identified. Most of the metabolites that circulate in the blood are sulfates of 3α, 5β-tetrahydro-LNG, while excretion occurs predominantly in the form of glucuronides. The results from *in vitro* studies (A02495) have demonstrated that oxidative metabolism of LNG is catalyzed by CYP enzymes, especially CYP3A4 (see **Section 2.3.1**). The suggested main metabolic pathway of LNG is shown in **Figure 6**.

  Figure 6 Main metabolic pathway of LNG



Reference ID: 3226051

- **Excretion**
  Following i.v. 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. Only trace amounts of LNG are excreted in unchanged form. The metabolites are excreted with feces and urine at an excretion ratio of about 1.

2.2.5 Does silver ring attached to LCS12 result in an elevated systemic silver exposure?

No. As noted under 2.2.1, detection and differentiation of the LCS12 T-body by ultrasound is facilitated by the addition of a silver ring in the upper part of the vertical stem in the T-body. The silver ion concentrations were measured in 24 subjects in the Phase 3 study at baseline and around 1 and 3 years after LCS12 insertion. Serum concentrations of silver were below the lower quantification of 1 µg/L. In addition, no adverse systemic or local effects arising from the silver profile of LCS12 were observed.

2.2.6 Is there a depot effect after LCS12 removal?

Not likely. No study was conducted to measure the LNG serum concentration after LCS12 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. Specifically, for a body weight of 51 kg (5th percentile of the body weight distribution from the Phase 3 study) and 99 kg (95th percentile) the clearance values were 76% and 152% of the typical values, respectively, based on the median body weight. Nonetheless, the effect of body weight is not considered as clinically relevant given its low impact on the safety and efficacy of LCS12.

Based on the data from the Phase 3 study, no additional safety issues were identified in women with BMI over 30 kg/m^2. In addition, the small size (n=244) of the subgroup of women with BMI $\geq$ 30 kg/m^2 together with high effectiveness of IUS in general does not allow for a detection of differences in the pearl index (PI) between the BMI subgroups. However, the widely overlapping 95% CIs between the subgroups give no evidence of differences in the PI based on the BMI.

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 LCS12.

Due to mainly local action of LCS12, the efficacy would not be compromised. Serum concentration of LNG could be elevated in women with impaired renal or hepatic function. However, considering the dose of LNG in LCS12 is about 10 times lower than that from LNG-containing oral contraceptives such as Levonest®, no critical concentrations are expected during the use of LCS12 in women with renal or hepatic impairment.

Pediatric Subjects

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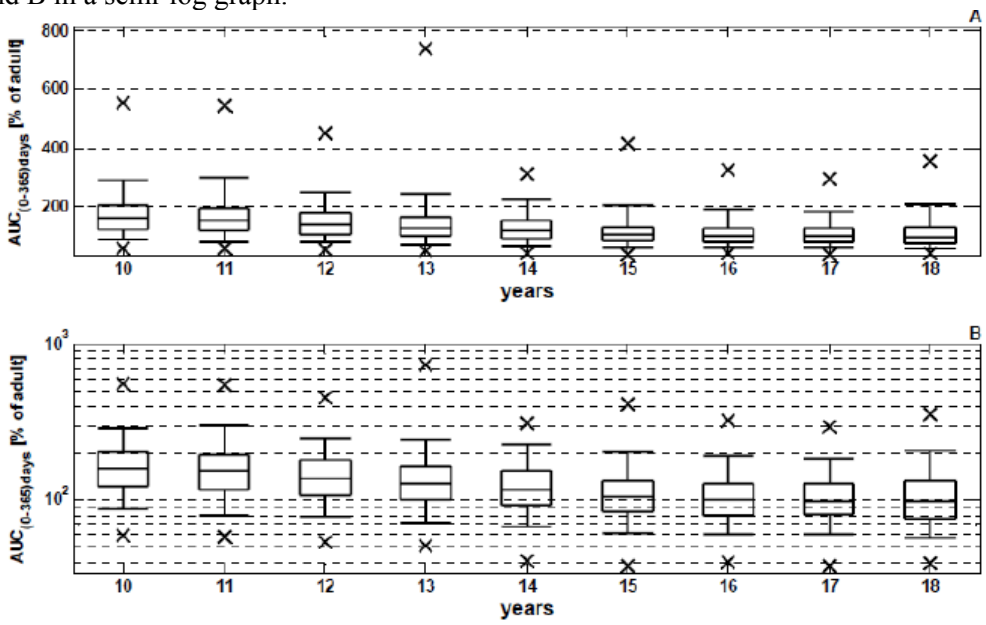
The Sponsor requested a partial waiver for pre-menarche children as they are not at risk of becoming pregnant. The Sponsor requested that the Pediatric Research Equity Act (PREA) requirements for postmenarchal pediatric subjects be deemed fulfilled by extrapolation of adult data. The Sponsor plans to conduct a multi-center, single-arm study to assess the safety, efficacy, discontinuation rate and
PK of LCS12 in 300 post-menarcheal female adolescents under 18 years of age for 1 year, and an optional 2-year extension phase. The Division will request the Sponsor submit the data once the study is completed in Europe.

A PBPK model was used to explore the PK properties of LNG in LCS12 in adolescents of various age groups. Based on the proposed model, PK parameters such as C_{max}, C_{365d} and $AUC_{0\text{-}365d}$ do not differ in girls between 15 and 18 years to a relevant extent. The difference of the median values is less than 10%. In girls between 10 and 15 years, an up to 1.6-fold increase of the PK parameters mentioned above with decreasing age was observed. The median PK parameters like C_{max}, C_{365d} and $AUC_{(0\text{-}365d)}$ increase on average maximally by 60% in a 10-year old girl in comparison to an adult women (30-year old). In **Figure 7**, the parameter $AUC_{0\text{-}365d}$ is presented in % of the respective value in a 30-year old woman. The details of the study can be found the in the individual review by Dr. Ping Zhao (see the appendix).

Figure 7: Age-dependence of $AUC_{(0\text{-}365d)}$ [% of typical adult]. Graph A presents data in a linear graph, and B in a semi-log graph.



*Top and bottom walls of each box represent the 75th and 25th percentiles. Whiskers (error bars) above and below each box indicate the 90th and 10th percentiles, and x represent the 95th and 5th percentiles.

2.4 EXTRINSIC FACTORS

No clinical DDI study was conducted under this NDA. Information from the *in vitro* DDI studies conducted with LNG in the current NDA submission is presented below:

2.4.1 Effects of Other Drugs on LNG

Data from *in vitro* studies (Study A02495) demonstrated that LNG is mainly metabolized by CYP3A4. Thus, drugs which are affecting the activity of CYP3A4 may change the PK of LNG.

<u>CYP isozymes involved in LNG metabolism</u>

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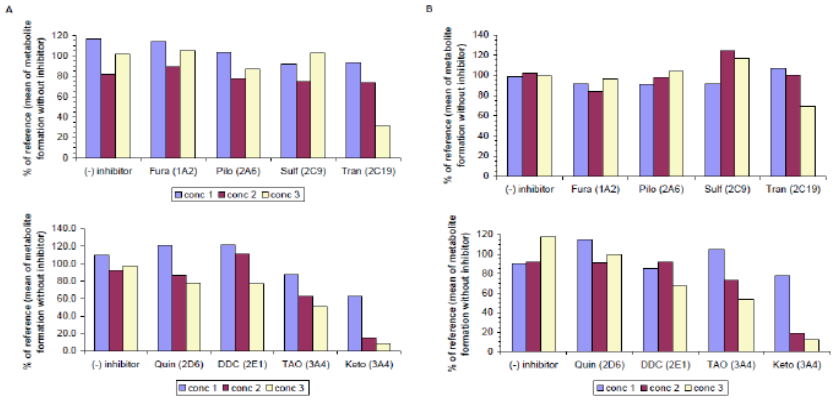
The involvement of CYP1A2, 2A6, 2C9, 2C19, 2D6, 2E1, and 3A4/5 in LNG metabolism was investigated with human liver microsomes using specific chemical inhibitors. **Figure 8** presents the effects of different inhibitors on the metabolism of LNG following incubation for 30 and 120 minutes. Based on these results, LNG is mainly metabolized by CYP3A4. A concentration dependent decrease in metabolite formation was observed in the presence of tranylcypromine (CYP2C19 inhibitor). However, significant inhibition was only observed at the highest concentration of 100 µM which is likely to affect other CYP isozymes in addition to CYP3A4 due to loss of specificity.

The involvement of CYP3A4 in LNG metabolism was further confirmed with CYP3A4-expressing isozyme (Figure not shown).

Figure 8 Effects of chemical inhibitors on the metabolism of LNG following incubation for 30 (A) and 120 (B) minutes with human liver microsomes



2.4.2 Effects of LNG on other Drugs

Data from i*n vitro* studies (Study A02495) suggested that LNG is unlikely to affect the metabolism of other drugs by CYP3A4/5, because C_{max} value of LNG from LCS12 was about four orders of magnitude lower than the determined IC_{50} value. In addition, LNG did not affect the metabolism of the other model substrates of CYP1A2, 2A6, 2C9, 2C19, 2D6 and 2E1 *in vitro*.

<u>Inhibitory effect of LNG on metabolism by CYP isozymes</u>

LNG was pre-incubated at different concentrations (0-250 µM) with human liver microsomes for 15 minutes followed by addition of the model substrate. The inhibition potential was determined by Radio-HPLC measuring the decrease of metabolite formation compared to control (without LNG). The IC_{50} value of LNG was determined for each CYP isozyme using respective model substrates.

LNG inhibited metabolism of testosterone, a substrate of CYP3A4 (IC50: 18.2-13.6 µM). There was no influence on other substrates (**Table 5**).

Table 5: Effect of LNG on metabolism of different model substrates with human liver microsomes

Model substrate	Conc.(µM)	CYP	Incubation time (min)	IC_{50}(µM)
Methoxyresorufin	1	1A2	-	>250
Coumarin	50	2A6	5	>250
Coumarin	50	2A6	20	>250
Tolbutamide	2.00	2C9	40	>250
Tolbutamide	2.00	2C9	120	>250
S-Mephenytoin	50	2C19	40	>250
S-Mephenytoin	50	2C19	120	>250

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Dextromethorphan	20	2D6	20	>250
Dextromethorphan	20	2D6	60	>250
Chlorzoxazone	50	2E1	2D	>250
Chlorzoxazone	50	2E1	60	>250
Testosterone	50	3A4	20	18.2
Testosterone	50	3A4	60	13.6

LNG concentration range: 2.5 ~250 μM

2.5 GENERAL BIOPHARMACEUTICS

2.5.1 Is the clinical formulation same to the TBM formulation?

No. Compared to Phase 3 formulation, minor modifications have been implemented for the TBM product, namely, the removal threads, the modified inserter and further minor modifications of the T-body. The clinical and TBM formulations of LCS12 are presented in **Table 6**. Per Biopharmaceutics reviewer Dr. Sandra Suarez Sharp, based on the level of changes in the TBM product, a bridging study is needed and the bridging for the formulation change can be supported by *in vitro* dissolution data. The Sponsor submitted the requested bridging data on May 17, 2012. Biopharmaceutics reviewer Dr. Sandra, Suarez Sharp agreed with the similarity between Phase 3 and TBM formulation as demonstrated by f2 test.

The formulations of LCS12 used in the Phase 2 and Phase 3 clinical studies were slightly different. (b) (4) Other changes were the addition of a silver profile (ring) and some modifications in the design of the T-body. Given that the safety and efficacy of LCS12 was mainly evaluated based on the Phase 3 data, the bridging between Phase 2 and Phase 3 formulations is not necessary.

Table 6 The clinical and TBM formulations of LCS12

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Component/description	Phase 2	Phase 3	TBM
Drug (b) (4) (b) (4)	(b) (4)		
(b) (4)			
Membrane (b) (4) (b) (4) Membrane thickness target Material			
(b) (4) Length			
T-Body Composition Dimensions Length of horizontal arm × vertical stem × diameter of vertical stem Silver profile			
Removal thread Composition Dimensions			
Inserter Insertion applicator			

2.6 ANALYTICAL SECTION

2.6.1 What bioanalytical methods are used to assess concentrations?

LNG serum concentration

LNG serum concentrations were determined with a validated radioimmunoassay method based on the specific antiserum preparation and tritium labeled LNG. The detailed analytical conditions are presented in **Table 7**.

Table 7 Radioimmunoassay for serum LNG concentration

Calibration range	10 ~ 2000 ng/L
Lower limit of quantitation (LLOQ)	30.0 ng/L
Upper limit of quantitation (ULOQ)	600 ng/L
Inter-assay Standard Precision (% CV)	≤ 4.6%
Inter-assay Standard Accuracy (% Bias)	98 ~ 102 %
Inter-assay QC precision (% CV)	7.2 ~ 14.0 %
Inter-assay QC Accuracy (% Bias)	89 ~ 102 %

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Stability in plasma at 4 ºC	at least 11 weeks
Stability in plasma at - 20ºC	2 years
Incurred sample stability	at least 44 month

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 8**.

Table 8 Fluoroimmunoassay for serum SHBG concentration

Calibration range	6.30 ~ 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 ~ 101 %
Inter-assay QC precision (% CV)	4.5 ~ 7.3 %
Inter-assay QC Accuracy (% Bias)	90 ~ 113 %
Stability in plasma at - 20ºC	at least 34 months

Acceptable criteria and assay performance for each analyte were in compliance with the *bioanalytical Method Validation Guidance* and the bioanalytical methods were found to be acceptable.

3 DETAILED LABELING RECOMMENDATIONS

1 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Reference ID: 322605

4 APPENDICES

4.1 INDIVIDUAL STUD REVIEW

4.4.1 Phase III Study A52238 (review focus on LCS12 PK characterization) :

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

Protocol No:	310442
Phase:	3
Principal Investigator:	138 principal investigators
Clinical Study Center:	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:	20 AUG 2007 to 08 JUN 2011

BACKGROUND:
No clinical pharmacology study was conducted with LCS12. The characterization of LCS12 pharmacokinetic (PK) profile was mainly based on the Phase 3 study by non-compartmental analysis via intense PK sampling in a sub-population of 12 subjects (subset 3) and by population PK analysis via sparse sampling at one sample per subject. The population PK analysis was reviewed separately in the population PK study reports. Therefore, the current individual study review mainly focused on non-compartmental analysis of LCS12 using data from subset 3.

OBJECTIVE:
Characterization of the PK profile of levonorgestrel (LNG) released from LCS12

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
This was a subset study (PK study) in a multi-center, open label, Phase 3 trial examining the safety and contraceptive efficacy of LCS12 and LCS16 for three years of use.

Twenty four (24) subjects were planned for the subset study with 12 subjects per treatment arm (LCS12 and LCS16). One LCS with either 12 µg/day (LCS12) or 16 µg/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. During the 3 years treatment, concentration of LNG and SHBG were measured at baseline, at day 1, 3, 7 and 14 after start of treatment and thereafter at every regular visit (3, 6, 9, 12, 18, 24, 30, and 36 month)

Thirteen (13) subjects are valid for PK analysis, 7 subjects from treatment arm LCS12 and 6 subjects from treatment arm LCS16. The subjects not eligible for PK analysis either did not have 3- year LNG and SHBG samples or had more than one missing sample around t_{max}

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FORMULATION

Treatment arms	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)
LCS12	G04209F	12	13.5	28 x 30	2.8	12	3.80
LCS16	G04209G	16	19.5	28 x 30	2.8	18	3.80

BIOANALYTICAL METHOD

Serum concentrations of LNG and SHBG were analyzed in (b) (4)

- **Determination of LNG concentration in serum**

LNG was determined in human serum with a validated radioimmunoassay 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 (3H-LNG) was measured by means of a scintillation counter. The detailed analytical conditions are presented in **Table 1**. Details of the method description and validation can be found in non-clinical study report A42971 and method validation reports A01291 and A05720.

Table 1 Radioimmunoassay for serum LNG concentration

Calibration range	10 ~ 2000 ng/L
Lower limit of quantitation (LLOQ)	30.0 ng/L
Upper limit of quantitation (ULOQ)	600 ng/L
Inter-assay Standard Precision (% CV)	≤ 4.6%
Inter-assay Standard Accuracy (% Bias)	98 ~ 102 %
Inter-assay QC precision (% CV)	7.2 ~ 14.0 %
Inter-assay QC Accuracy (% Bias)	89 ~ 102 %
Stability in plasma at 4 ºC	at least 11 weeks
Stability in plasma at - 20ºC	2 years
Incurred sample stability	at least 44 month

- **Determination of SHBG in serum**

The concentration of SHBG in human serum was determined with a validated method by means of a commercially available 96-well plate, time-resolved, fluoroimmunoassay (TRFIA) obtained from (b) (4) The detailed analytical conditions are presented in **Table 2**. Details of the method description and validation can be found in Nonclinical Study Report A42971 method validation report A11596 and A33598.

Table 2 Fluoroimmunoassay for serum SHBG concentration

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Calibration range	6.30 ~ 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 ~ 101 %
Inter-assay QC precision (% CV)	4.5 ~ 7.3 %
Inter-assay QC Accuracy (% Bias)	90 ~ 113 %
Stability in plasma at - 20ºC	at least 34 months

DATA ANALYSIS

The PK parameters C_{max}, C_{av}, C_{min}, C_{last}, t_{max}, t_{last}, t_{min} and $AUC_{(0\text{-}tlast)}$ for LNG were calculated using the model-independent (compartment-free) method in accordance with pertinent company standards using WinNonlin, version 4.1 (Pharsight Corporation) in conjunction with the Automation Extension (version 2.6.0.1, Bayer AG).

RESULTS

- **Serum LNG concentration**

After insertion of LCS12, an arithmetic mean of maximum serum concentration (C_{max}) of LNG was 192 ± 105 ng/L, reached after 2 days (median). Thereafter, the serum concentration of LNG decreased slowly to the mean value (C_{ave}) of 75 ± 32 ng/L. During the LCS12 treatment period of 3 years, a mean minimum concentration (C_{min}) of 48 ± 30 ng/L was observed (**Table 3).** The mean and individual LNG concentration-time profiles are presented **Figure 1** and **Figure 2**, respectively.

Table 3 Arithmetic Mean (SD) PK parameters of LNG observed after insertion of LCS12 (N=7*)

$AUC_{(0\text{-}tlast)}$ (ng·d/L)	**C_{max}** (ng/L)	**t_{max}** (d)	**C_{ave}** (ng/L)	**C_{min}** (ng/L)	**t_{min}** (d)	**C_{last}** (ng/L)	**t_{last}** (d)
82083 (34674)	192 (105)	2.00 (1.00-16.0)	75 (32)	48 (30)	733 (546-1085)	72 (29)	1085 (1083-1135)

- For all PK parameters the arithmetic means with the standard deviation (SD, in parentheses) are given, except for tmax, tmin and tlast, where the median and the range (in parentheses) are provided.
- Cmax = maximum observed concentration
- tmax = time to reach Cmax
- AUC(0-tlast) = area under the drug concentration vs time curve from time 0 to the last data point >LLOQ
- Cav = average steady state concentration (AUC(0-tlast)/ tlast)
- Cmin = minimum observed concentration
- Clast = last observed concentration above the LLOQ
- tmin = time to reach minimum observed concentration
- tlast = time of last concentration above the LLOQ
- * includes 2 subjects each with one concentration value < LLOQ (Subject 160734 and Subject 160753) which were set to ½ LLOQ for evaluation

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Figure 1 Arithmetic mean (±SD) LNG concentrations-Time profile following insertion of LCS12

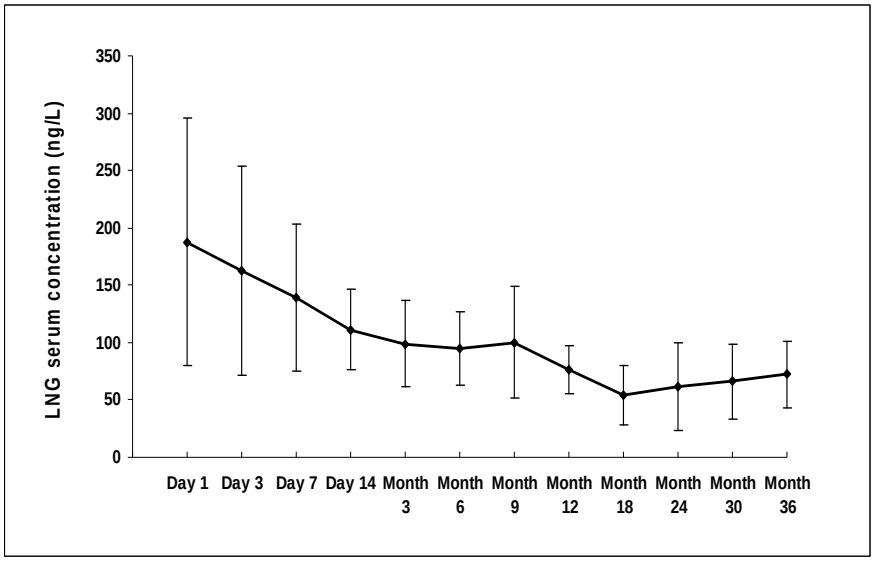
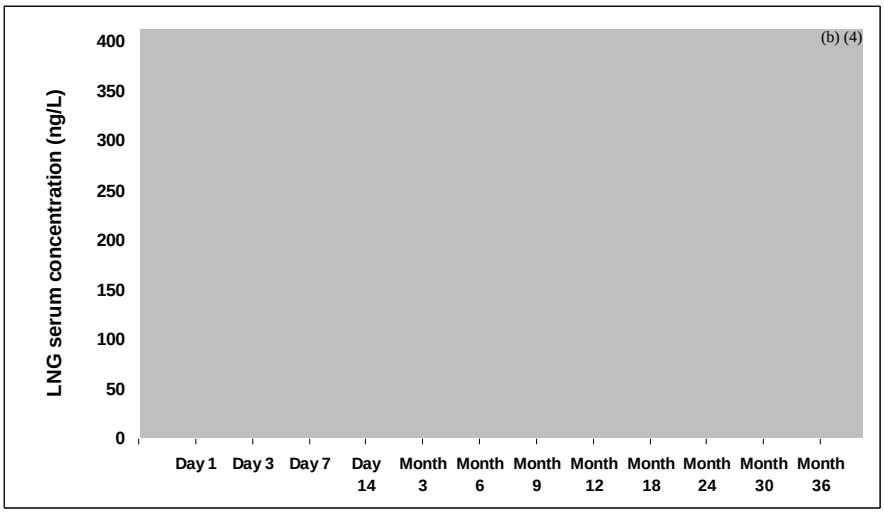


Figure 2 Individual LNG concentrations-Time profile following insertion of LCS12



Reviewer's notes:
LNG serum concentrations at week 2 and 30 month were missing for subject 160729 and subject 160734, respectively.

- **Serum SHBG concentration**

After insertion of LCS12, SHBG serum concentrations showed nearly stable concentration values over the 36-month period from a mean baseline concentration of 67.1 nmol/L to 59.7 nmol/L at the end of observation. A slight decline of SHBG was observed during the first 1 to 2 weeks after insertion (**Figure 3** and **Figure 4**). After that, nearly plateau-like serum levels were observed with a tendency to increase towards the end of the observation period. The mean SHBG concentrations during 3 years of LCS12 treatment are summarized in **Table 4**.

Figure 3 Arithmetic mean (±SD) SHBG concentrations-Time profile following insertion of LCS12

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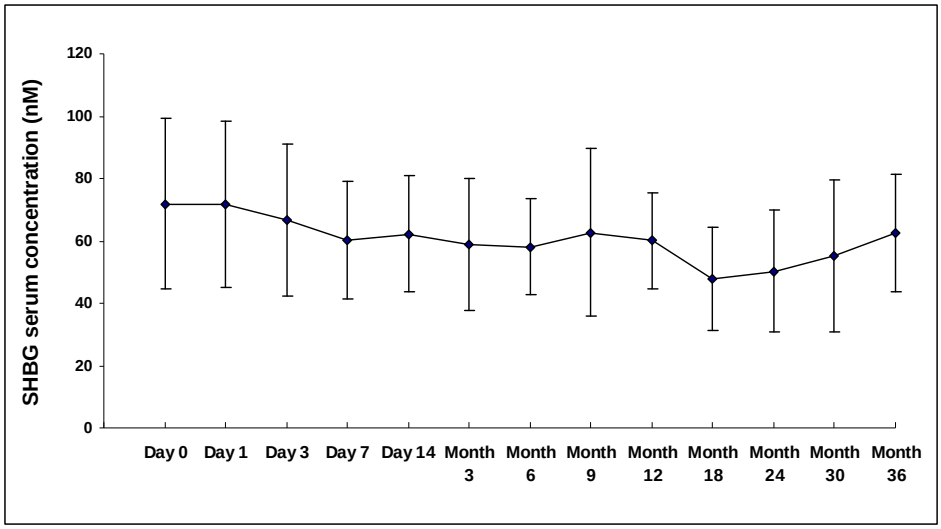

Figure 4 Individual SHBG concentrations-Time profile following insertion of LCS12

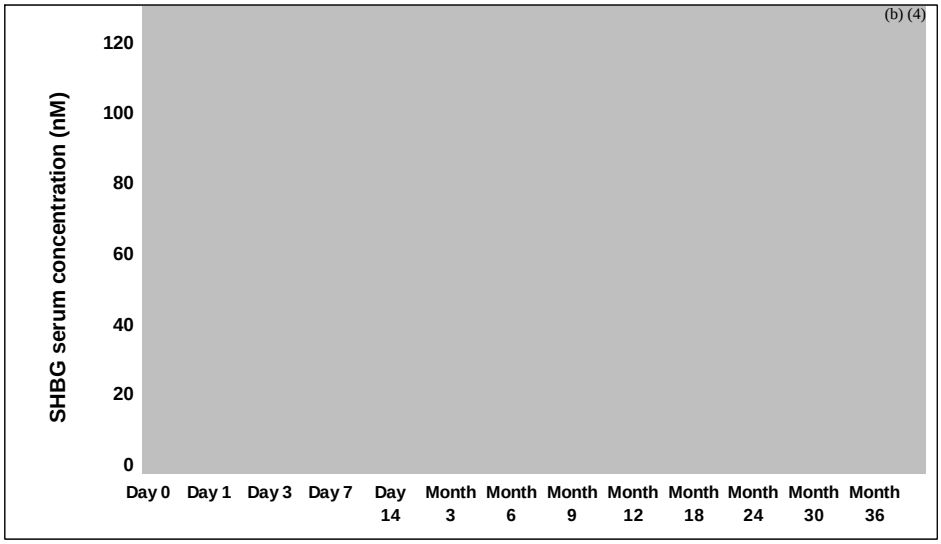

Table 4 Arithmetic Mean (CV%) SHBG concentrations after insertion of LCS12 (N=7)

	Baseline	**C (0.5 month)**	**C (3 month)**	**C(6 month)**	**C(12 month)**	**C(18 month)**	**C(24 month)**	**C(36 month)**
Mean (nM)	72	59	59	58	60	48	50	62
SD	28	18	21	15	15	17	20	19

Reference ID: 3226051

4.4.2 Population study report: Study A57551

Exploratory population pharmacokinetic analysis of levonorgestrel (LNG) in the multi-center, open, randomized, dose finding phase II study 308901 to investigate for a maximum of three years ultra low dose LNG contraceptive intrauterine systems (LCS) releasing in vitro 12 µg/24h and 16 µg/24h of LNG compared to MIRENA® in nulliparous and parous women in need of contraception

OBJECTIVE

The primary objectives of this PK evaluation were

- to define a structural PK model for LNG in the Phase 2 study (308901 or A46796) including the description of the release from the intrauterine system (IUS, Mirena®, LCS12 or LCS16) and the resultant LNG serum concentration taking into account the interaction with sex hormone binding globulin (SHBG)
- to characterize the inter-individual variability of the derived PK parameters of LNG in these specific populations
- if appropriate, to evaluate possible covariates influencing the PK of LNG.

DATA

- Phase 2 study (308901 or A46796): Serum LNG concentrations, serum SHBG concentrations as well as residual content data from the IUSs (Mirena®, LCS12 and LCS16).

  The study population consisted of parous or nulliparous women of 21 to 40 years of age (inclusive). Number of analyzed subject was 738 (LCS12: 239, LCS16: 245, Mirena®: 254). Within each dose group (LCS12, LCS16, Mirena®), additionally three subsets were formed:
  - Subset 1: Ovarian and cervical function studied in 60 subjects (~20 per treatment arm). Serum LNG and SHBG were analyzed at day 1, 3, 5, 7, 9 and 11 during the first year, and then at day 1 and 12 during the second and the third year after insertion
  - Subset 2: endometrial histology studied in 90 subjects (~30 per treatment arm)
  - Subset 3: detailed PK of LNG studied (~12 subjects per treatment arm). Serum LNG and SHBG were determined at baseline and at day 1, 3, 7 and 14, month 1, 6, 12 , 18, 24, 30 and 36 month after start of treatment.
  - Subset 4: All subjects included in the analysis not belonging to either of the subsets defined above are referred to as subset 4.

  LNG and SHBG were measured in all subjects at the end of the study.

- Phase 1 study 92085:
  In the open, single dose, crossover study 92085, the absolute bioavailability of LNG from MICROLUT and dose linearity of LNG PK in 18 healthy, young women (planned: 20 to 40 years of age) was assessed. Four different treatments were administered: oral doses of 0.03 mg, 0.09 mg and 0.27 mg LNG (1 to 9 coated tablets MICROLUT) and an intravenous dose (injected over 30 seconds) of 0.09 mg LNG. In this evaluation only the intravenous administration is considered.

METHODS

Graphical visualization and population PK/PD modeling based on nonlinear mixed-effects modeling was the principal analysis technique. The data were analyzed using NONMEM, version VI level 2.0 and NONMEM version 7.1.2 (Icon Development Solutions, Ellicott City, Maryland USA) together with SAS, S-PLUS, R or Matlab for goodness of fit assessment and covariate model building. The first order conditional estimation with interaction (FOCE with η-ε interaction) method in NONMEM was used for all analyses.

Reference ID: 3226051

RESULTS

- **Base model development**
  The release of LNG from Mirena® was modeled by a first-order release. In contrast to Mirena®, a relatively high initial drop of the LNG release for LCS12 and LCS16 was observed. Since the (b) (4) two release processes were assumed and supported by the model: one zero-order and one first-order release with a time-dependent release rate. The PK of LNG was described by a two-compartment model under consideration that only the free fraction was cleared (interaction with SHBG). The inhibitory effect of LNG on SHBG was modeled by introduction of a delay compartment. The production and elimination of SHBG were described by a one-compartment model.
- **Covariate model development**
  Inter-individual variability was identified on the clearance parameter as well as on the SHBG baseline value. The later part of the model development was based only on data from the PK subset (subset 3) of study 308901 and on data from study 92085 (subjects with intravenous treatment of 0.09 mg LNG) since modeling including inter-individual variability on all data was not possible. Covariate analysis revealed no effect of body weight on the clearance of LNG and on the SHBG baseline concentration in the range of this dataset (51.2 – 105 kg, N=55). No other covariate effect such as age, height, body mass index (BMI), lean body mass (LBM) and body fat on the clearance and on the baseline was found.
- **Final model development**
  The final base model is the final model. A schematic representation of the final PK/PD model LNG/SHBG is shown in **Figure 1**. The final parameters and parameters precisions are listed in **Table 1**. The goodness-of-fit plots are presented in **Figure 2**.

Figure 1 Model scheme of the final population PK/PD model LNG/SHBG for Mirena® and both LCS treatments LCS12 and LCS16. Solid lines denote a mass flow, dashed lines indicate an indirect influence. The grey arrow is only valid for LCS12 and LCS16.

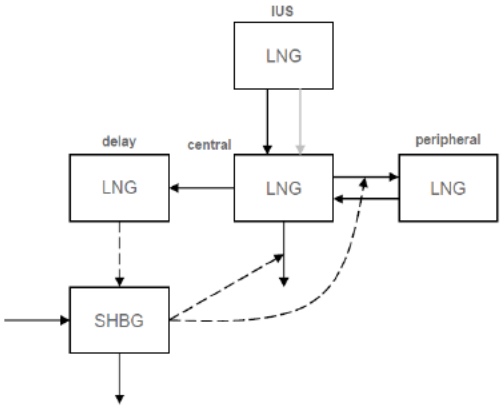

Table 1 Population parameter estimates together with their standard errors and confidence intervals of the final PK/PD covariate model LCS LNG/SHBG

Reference ID: 3226051

Parameter	Notation model files	Unit	Estimate	RSE [%][a]	LLCI[b]	ULCI[c]	Analyte	Description
Fixed effects								
$C12_{LCS12}$	C12 LCS12	ng/h	213	2.9	201	225	LNG	zero-order release rate LCS12 (release 1)
$C12_{LCS16}$	C12 LCS16	ng/h	292	3.8	270	314	LNG	zero-order release rate LCS16 (release 1)
$C12_{Mirena}$	C12 Mirena	1/h	16.2	0.2	16.1	16.3	LNG	first-order release rate Mirena
C13	C13	-	0.0675	22.5	0.0371	0.0979	LNG	release rate for release 2 (LCS12 and LCS16)
T1	T1	h	3910	24.7	1982	5838	LNG	time parameter for drop in release 2 (LCS12 and LCS16)
V2	V2	L	21.0	5.5	18.7	23.3	LNG	volume central compartment
CL	CL	L/h	240	3.7	222	258	LNG	clearance central compartment
V3	V3	L	4170	6.9	3598	4742	LNG	volume peripheral compartment
Q3	Q3	L/h	633	6.2	555	711	LNG	inter-compartmental clearance
τ_{LNG}	TAU	h	24[e] FIX				SHBG	delay of effect of LNG on SHBG
R_I	RI	L/nmol	0.242	18.3	0.153	0.331	SHBG	factor of inhibition SHBG by LNG
k_{out}	KOUT	1/h	0.00538[e] FIX				SHBG	elimination rate of SHBG
SBL	SBL	nmol/L	56.0	2.2	53.5	58.5	SHBG	SHBG baseline
Random effects								
Inter-individual variability[d]								
IIV_CL (CV)		%	29.2	24.6	20.8	35.7	LNG	inter-individual variability of the clearance
IIV_SBL (CV)		%	50.2[g]	37.2	25.4	66.3	SHBG	inter-individual variability of the SHBG baseline
Residual error								
(b) (4) LNG serum (CV)		%	20.0	9.9	17.9	21.9	LNG	proportional residual error LNG serum
(b) (4) SHBG		%	20.0	15.0	16.8	22.8	SHBG	proportional residual error SHBG
(b) (4) Mirena content		%	0.4	82.3[f]	nan	0.680	LNG	proportional residual error Mirena content
(b) (4) LCS12 content		%	1.7	59.7[f]	nan	2.52	LNG	proportional residual error LCS12 content
(b) (4) LCS16 content		%	2.2	42.7[f]	0.854	3.041	LNG	proportional residual error LCS16 content

a RSE = relative standard error, expressed as percentage of estimate
b LLCI = lower limit of the 95% confidence interval (estimation - 2x standard deviation)
c ULCI = upper limit of the 95% confidence interval (estimation + 2x standard deviation)
d the coefficient of variation (CV) is calculated here by an approximation (first-order Taylor expansion) which is the square root of the variance
e fixed to appropriate value (population PK/PD analyses from project FC Patch low)
f high standard error due to low number of observations
g since CV>50%, calculation of CV with correct formula: 53.5%

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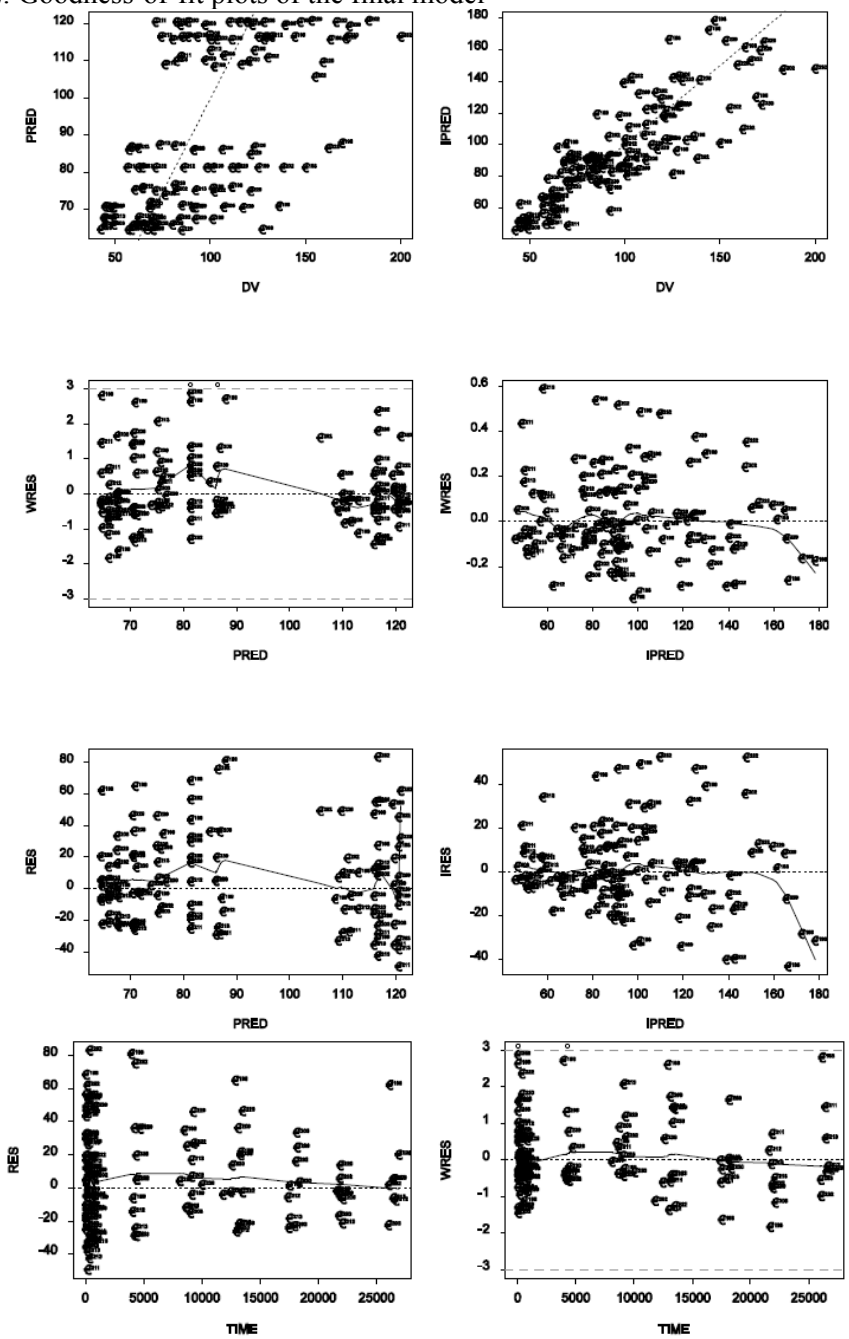
Figure 2 LCS12: Goodness-of-fit plots of the final model



- **Model qualification**
  The final PK/PD model LNG/SHBG was qualified
  - Internally: with data from subset 3 of the Phase 2 study (308901 or A46796, used in the final model development)
  - Externally: with the remaining subsets 1, 2 and 4 of study 308901 (not used in the final model development).

  A visual predictive check (VPC) was performed by comparing the 90% prediction intervals of simulated concentrations using the final model with the observed concentrations. The medians of

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observed data were generally well centered in the simulated 90% prediction interval over the treatment period and variability of the observed data were adequately described using IPRED, indicating that the model describes the data well (Figures not shown).

CONCLUSIONS

In the final population PK/PD model, the PK of LNG after the insertion of an LNG releasing IUS (Mirena®, LCS12 or LCS16) was described taking the interaction with SHBG into account. For the release from Mirena® one release process was sufficient in the model approach, whereas for the LCS12 and LCS16 two different release processes were modeled (b) (4) No effect of body weight or other covariates on the clearance of LNG and the SHBG baseline was found in the covariate analysis (conducted on the same reduced dataset used for the final base model development).

Reviewer's Comments:

- *The population PK-PD model developed by the Sponsor seems to be reasonable.*
- *The LNG serum concentrations from LCS12 seem to be under-estimated at the high concentration range.*

Population study report: Study A57552

Exploratory population pharmacokinetic analysis of levonorgestrel (LNG) in the multi-center, open, randomized phase III study 310442 to assess the safety and contraceptive efficacy of two doses (in vitro 12 µg/24h and 16 µg/24h) of ultra low dose LNG contraceptive intrauterine systems (LCS) for a maximum of 3 years in women 18-35 years of age

OBJECTIVE

The primary objectives of this PK evaluation were

- to apply the population PK/PD model developed in study A57551 to data from Phase 3 study (310442 or A52238)
- to investigate the impact of the covariate body weight and other covariates if appropriate,
- to estimate individual total and unbound LNG serum concentrations after 3 months, 1 year, 2 years and 3 years (C3 months, C1 year, C2 years, C3 years). The unbound LNG serum concentration is calculated using SHBG and total LNG serum concentrations.

DATA

Phase 3 study (310442 or A52238): Serum LNG concentrations, serum SHBG concentrations as well as residual content data from LCS12 and LCS16.

- LNG and SHBG concentrations

Serum concentrations of LNG and SHBG were monitored by sparse blood sampling, i.e., a blood sample was taken at one of the interim study visits during treatment per each study subject. A detailed determination of the LNG and SHBG serum concentration - time course were conducted in subset 3 where blood samples were collected at baseline and at day 1, 3, 7 and 14, month 1, 6, 12, 18, 24, 30 and 36 month after start of treatment. In addition, a blood sample for the determination of serum LNG and SHBG concentration was taken from all subjects who prematurely discontinued the study.

In addition to the above variables studied in the whole study population, additional variables were studied in 4 subsets in (pre)selected centers. Evaluations of efficacy such as ovarian and cervical function or endometrial histology were conducted in subsets 1 and 2A, PK in subset 3 and safety in subsets 2B and 4.

- Subset 1 (S1): Ovarian and cervical function studied in 40 subjects (20/treatment arm)
- Subsets 2A (S2A) and 2B (S2B): Endometrial histology studied in 60 subjects (30/ treatment arm) (S2A), and assessment of hemostatic factors (S2B) (same 60 subjects)
- Subset 3 (S3): Detailed pharmacokinetics studied in 24 subjects (12/treatment arm)
- Subset 4 (S4): Bone mineral density (BMD) studied in 200 subjects (100/treatment arm)

All subjects included in the analysis not belonging to either of the subsets defined above are referred to as subset 9.

- Residual content from LCS12 and LCS16

The release of LNG from the LCS dose variants were determined by means of *ex vivo* residual content analysis of used LCSs collected from 690 (planned) randomly selected subjects (345 per treatment arm) who have completed the full 3 years of treatment and LCSs from all subjects discontinuing the study prematurely.

METHODS

Graphical visualization and population PK/PD modeling based on nonlinear mixed-effects modeling was the principal analysis technique. The data were analyzed using NONMEM, version VI level 2.0 and NONMEM version 7.1.2 (Icon Development Solutions, Ellicott City, Maryland USA) together with SAS, S-PLUS, R or Matlab for goodness of fit assessment and covariate model building. The first order

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conditional estimation with interaction (FOCE with η-ε interaction) method in NONMEM was used for all analyses.

RESULTS

- **Base model development**
  The population PK/PD model developed based on the Phase 2 study (308901 or A46796) was applied to data from the Phase 3 study (310442 or A52238). The visual predictive check (VPC) showed that the model described the data quite well. Nevertheless, optimization of the release parameters was necessary. The typical release of LCS16 was approximately 16.8% higher in the Phase 3 study (C12 = 341 ng/h) compared to Phase 2 study (C12 = 292 ng/h), if only the zero-order release of the two-release-approach is compared. Additionally the SHBG baseline was estimated.

- **Covariate model development**
  In the range of age (18 to 35 years), no correlation of AGE and CL or SHBG baseline (SBL) was observed in the diagnostic plots. The influence of the covariates including body weight (WGHT), body mass index (BMI), lean body mass (LBM) and body fat (FAT) was tested for the subjects of all subsets based on the final base model. Body weight was found to have the highest impact on CL, but no significant impact on SBL. Thus the final population PK/PD covariate model LNG/SHBG had the covariate body weight included. It was calculated that for a body weight of 51 kg (5th percentile of the body weight distribution from the Phase 3 study) and 99 kg (95th percentile) the clearance values were 76% and 152% of the typical value, respectively, based on the median body weight. The change of the clearance value per kg was approximately 1.6% of the typical value.

- **Final model development**
  The final covariate model is the final model. The final parameters and parameters precisions are listed in **Table 1**. The goodness-of-fit plots for final model on LNG serum concentrations are presented in **Figure 1**.

Table 1 Population parameter estimates together with their standard errors and confidence intervals of the final PK/PD covariate model LCS LNG/SHBG

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Parameter	Notation model files	Unit	Estimate	RSE [%][a]	LLCI[b]	ULCI[c]	Analyte	Description
Fixed effects								
$C12_{LCS12}$	C12 LCS12	ng/h	213	1.3	207	219	LNG	zero-order release rate LCS12 (release 1)
$C12_{LCS16}$	C12 LCS16	ng/h	341	1.1	333	349	LNG	zero-order release rate LCS16 (release 1)
$C13$	C13	-	0.0441	10.0	0.0352	0.0530	LNG	release rate for release 2 (LCS12 and LCS16)
FC_1	FC1	h	70440[e] FIX				LNG	correlation factor 1 for T1=FC1*(C13–FC2))
$FC_{2,LCS12}$	FC2 LCS12	-	0.0242	7.0	0.0208	0.0276	LNG	correlation factor 2 for T1=FC1*(C13–FC2)) (LCS12)
$T1_{LCS12} = FC_1 \cdot (C13 - FC_{2,LCS12})$	T1 LCS12	h	= 1402				LNG	time parameter for drop in release 2 (LCS12)
$FC_{2,LCS16}$	FC2 LCS16	-	0.0151	9.7	0.0122	0.0180	LNG	correlation factor 2 for T1=FC1*(C13–FC2)) (LCS16)
$T1_{LCS16} = FC_1 \cdot (C13 - FC_{2,LCS16})$	T1 LCS16	h	= 2043				LNG	time parameter for drop in release 2 (LCS16)
$V2$	V2	L	21.0[f] FIX				LNG	volume central compartment
CL	CL	L/h	240[f] FIX				LNG	clearance central compartment
$V3$	V3	L	4170[f] FIX				LNG	volume peripheral compartment
$Q3$	Q3	L/h	633[f] FIX				LNG	inter-compartmental clearance
τ	TAU	h	24[f] FIX				SHBG	delay of effect of LNG on SHBG
R_I	RI	L/nmol	0.242[f] FIX				SHBG	factor of inhibition SHBG by LNG
K_{out}	KOUT	1/h	0.00538[f] FIX				SHBG	elimination rate of SHBG
SBL_{low}	SBL 1/16	nmol/L	41.6	9.9	33.3	49.9	SHBG	SHBG baseline (group 1[g])
SBL_{medium}	SBL 1,3,4,9/12; 2,9/16	nmol/L	59.1	1.3	57.6	60.6	SHBG	SHBG baseline (group 2[g])
SBL_{high}	SBL 2/12; 3,4/16	nmol/L	68.0	4.8	61.5	74.5	SHBG	SHBG baseline (group 3[g])
$c_{WGHT,CL}$	COV WGHT on CL	-	0.0158	5.4	0.0141	0.0175	LNG	covariate body weight on CL
Random effects								
Inter-individual variability[d]								
IIV_CL (CV)		%	19.7	28.9	12.8	24.7	LNG	inter-individual variability of the clearance
IIV_SBL (CV)		%	37.3	17.1	30.3	43.2	SHBG	inter-individual variability of the SHBG baseline
Residual error								
(b) (4) LNG serum (CV)		%	40.2	5.2	38.1	42.3	LNG	proportional residual error LNG serum
(b) (4) SHBG (CV)		%	46.4	4.4	44.3	48.4	SHBG	proportional residual error SHBG
(b) (4) LCS12 content (CV)		%	3.3	20.3	2.56	3.93	LNG	proportional residual error LCS12 content
(b) (4) LCS16 content (CV)		%	2.4	12.1	2.12	2.71	LNG	proportional residual error LCS16 content

a RSE = relative standard error, expressed as percentage of estimate
b LLCI = lower limit of the 95% confidence interval (estimation - 2x standard deviation)
c ULCI = upper limit of the 95% confidence interval (estimation + 2x standard deviation)
d the coefficient of variation (CV) is calculated here by an approximation (first-order Taylor expansion) which is the square root of the variance
e fixed to appropriate value (current evaluation)
f fixed to value from the final PK/PD model 15775 (phase II model)
g group 1: subset 1 (LCS16); group 2: subsets 1, 3, 4 and 9 (LCS12) and subsets 2 and 9 (LCS16); group 3: subset 2 (LCS12) and subsets 3 and 4 (LCS16)

Figure 1 LCS12: Goodness-of-fit plots of the final model on LNG serum concentrations

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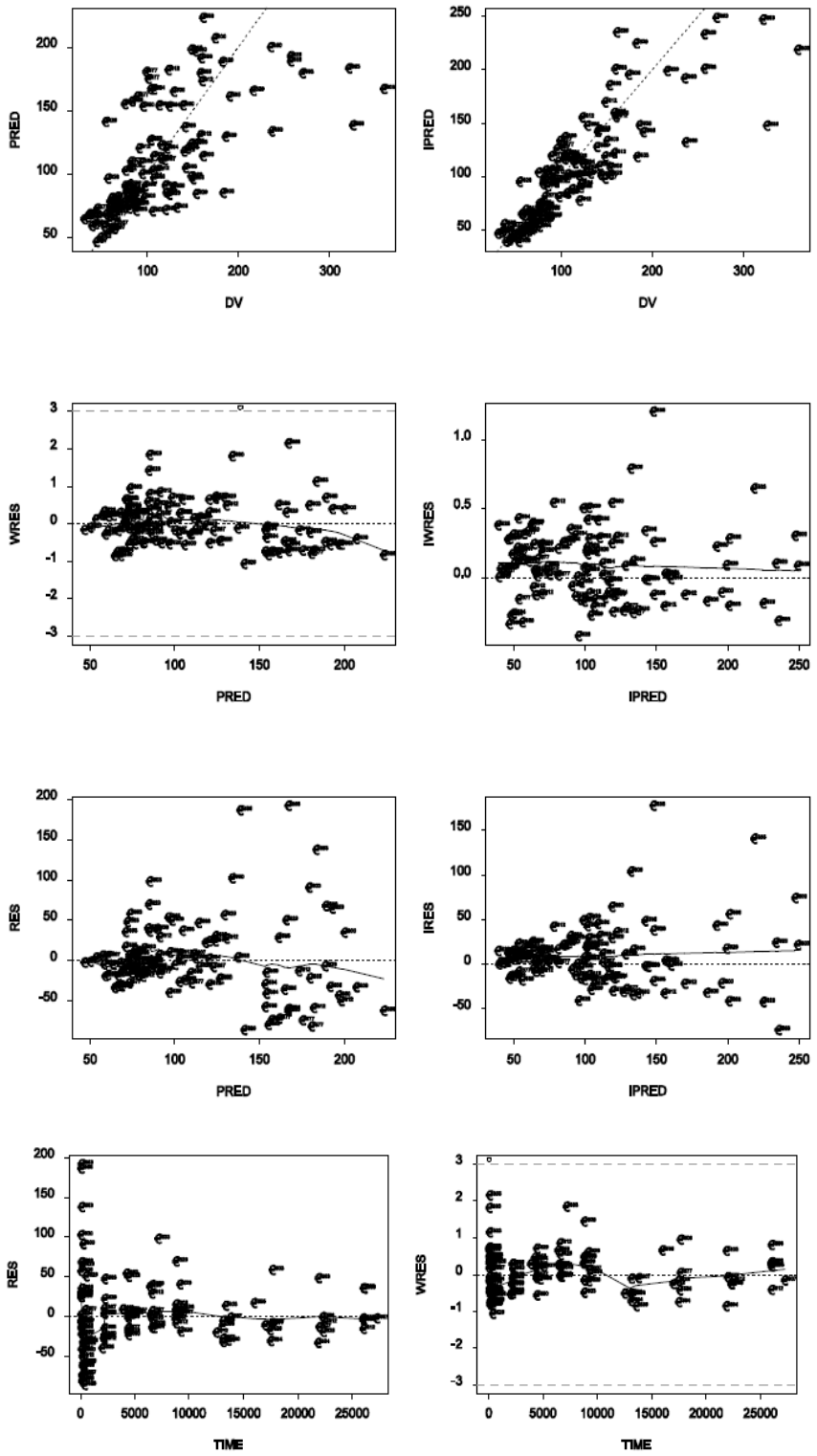
Subset 3



Subset 1

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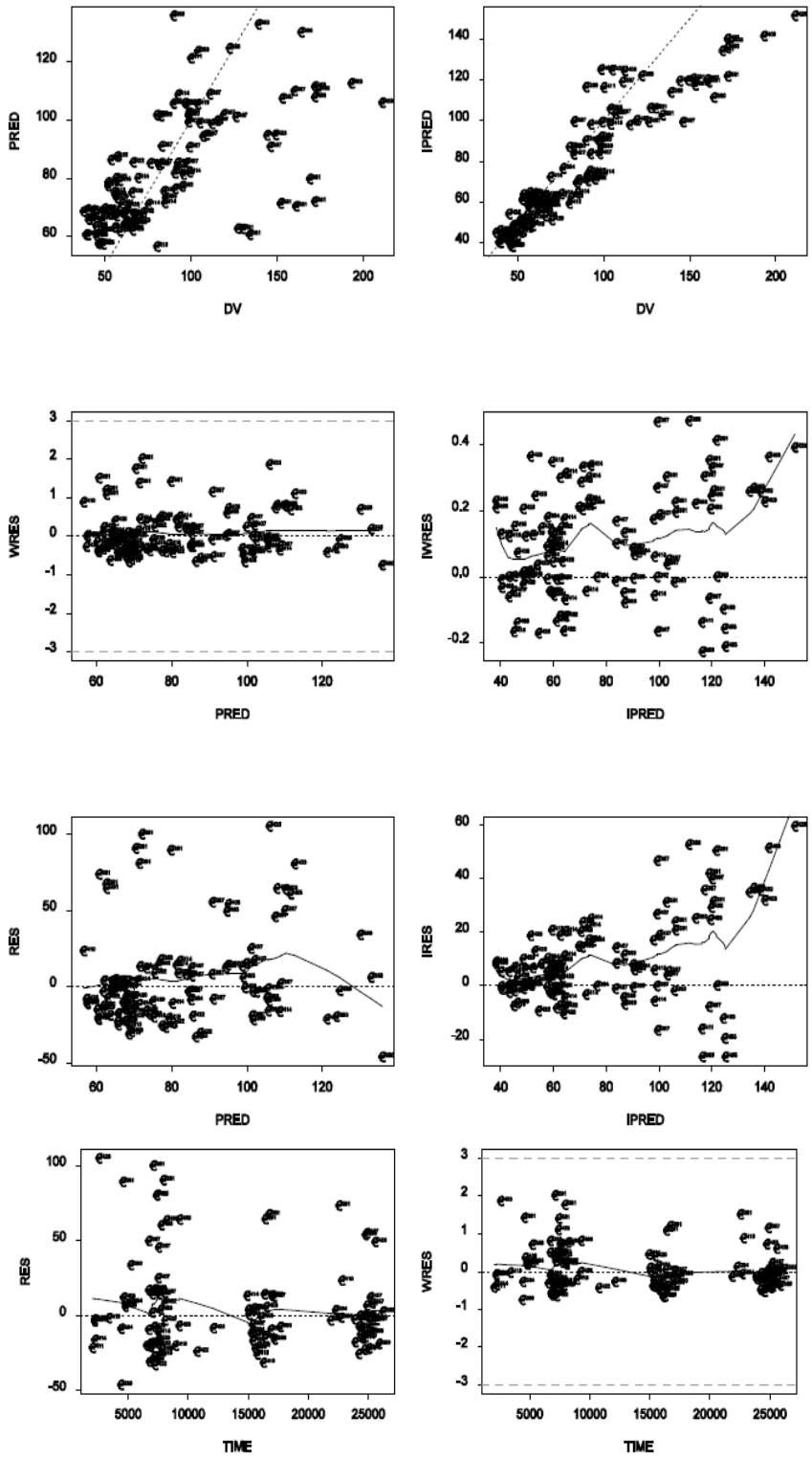
PRED
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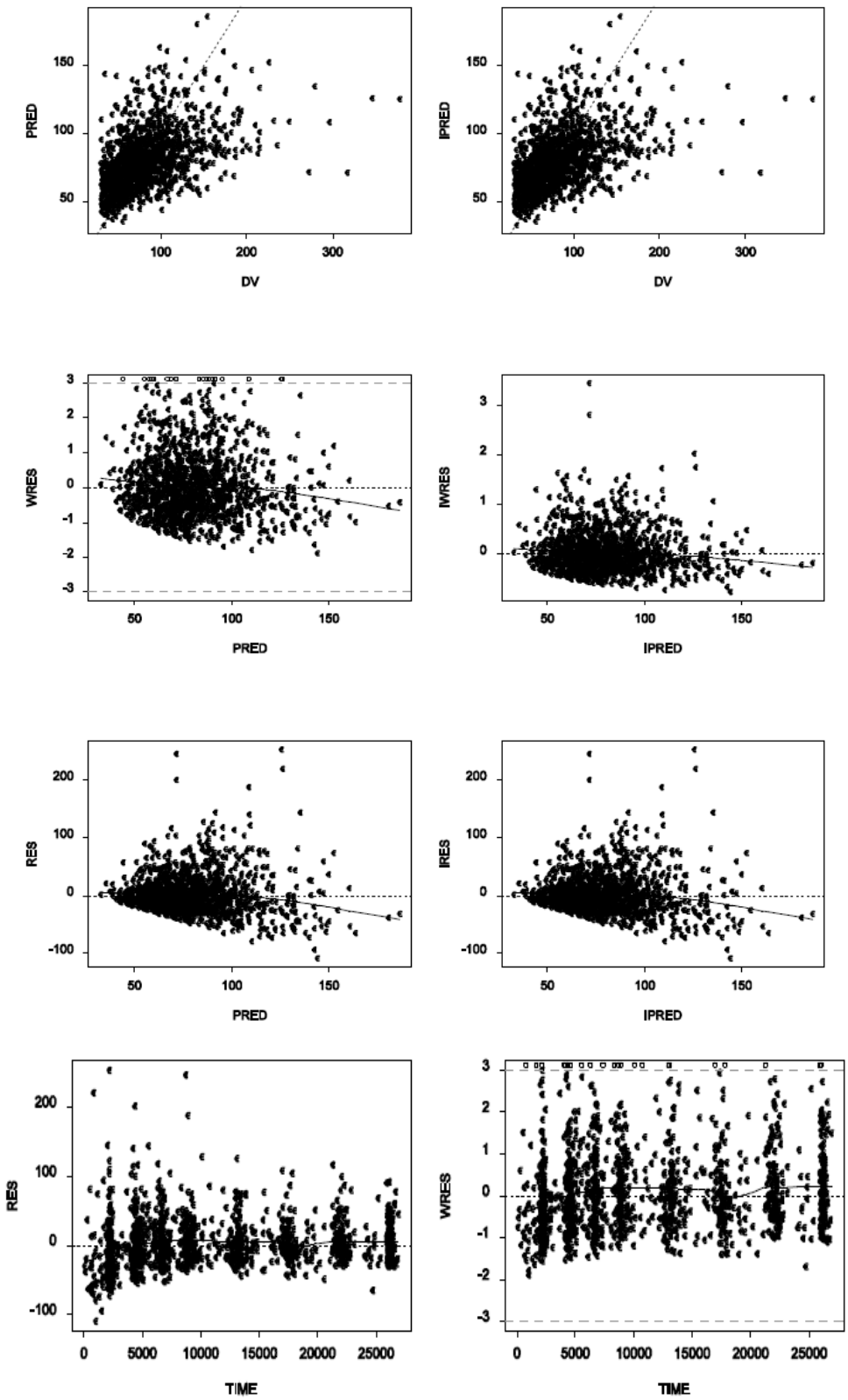
Subset 2, 4, 9



- **Model qualification**
  A visual predictive check (VPC) was performed by comparing the 90% prediction intervals of

simulated concentrations using the final model with the observed concentrations. The VPCs for total LNG serum concentration, LCS content (residual content) and SHBG concentration showed that the model describes the data well (Data not shown)

- **Estimation of individual total and unbound LNG serum concentrations**
  Based on this model with inter-individual variability applied to all subjects, among others individual total and unbound LNG serum concentrations after 3 months, 1 year, 2 years and 3 years as well as the typical in vivo release were estimated for the entire study population.
  The geometric mean of total LNG concentration for LCS12 after 3 months (91 days) was 99.8 ng/L, after 1 year 71.0 ng/L, after 2 years 64.3 ng/L and after 3 years 58.6 ng/L. The geometric mean of unbound LNG concentration for LCS12 after 3 months (91 days) was 1.49 ng/L, after 1 year 1.05 ng/L, after 2 years 0.947 ng/L and after 3 years 0.871 ng/L. The typical *in vivo* release from LCS12 after 1 day was 15.1 µg/24 h and declined to 5.36 µg/24 h after 3 years.

CONCLUSIONS

The population PK/PD model LNG/SHBG developed based on data from Phase 2 study could be applied to that in the Phase 3 study. The overall structural model was kept and estimation of the release parameters could overcome the misspecifications due to different batches used in the Phase 3 study (with a 6.8% higher initial content for LCS12 and a 4.1% higher initial content for LCS16 compared to the Phase 2 study). The covariate analysis revealed an effect of body weight on the CL of LNG in the study population with an approximate change of 1.6% of the typical clearance value per kg body weight. Individual average total and unbound LNG serum concentrations as well as typical *in vivo* release rates at defined time points were calculated. The geometric mean of total LNG concentration after 3 months was 99.8 ng/L and after 3 years 58.6 ng/L for LCS12.

Reviewer's Comments:

- *The population PK-PD model developed by the Sponsor seems to be reasonable.*
- *The predicted LNG serum concentrations using the proposed PK-PD model are consistent with the observed concentrations determined from sub-population in the Phase 3 study.*
- *The formulations of LCS12 used in the Phase 2 and Phase 3 studies were slightly different.* (b) (4) *Therefore, the re-estimation of release parameters based on the Phase 3 data is necessary.*
- *Body weight was identified as a significant covariate in the current analysis, but not for the analysis based on the Phase 2 data. The discrepancy might be due to the larger number of subjects in the current model development (N=2547 in the Phase 3 study vs. N=55 in the Phase 2 study).*
- *Based on the population PK analysis, the impact of body weight on LNG clearance was significant. Specifically, for a body weight of 51 kg (5th percentile of the body weight distribution from the Phase 3 study) and 99 kg (95th percentile) the clearance values were 76% and 152% of the typical values, respectively, based on the median body weight. Nonetheless, the effect of body weight is not considered as clinically relevant given its low impact on the safety and efficacy of LCS12. First, the contraceptive efficacy of LCS12 is believed to be primarily from the local action on uterus. Therefore, the change in systemic exposure is unlikely to affect the efficacy. Secondly, considering that the LNG serum concentration from LCS12 is about 10-fold less than that from LNG containing oral contraceptive, the increased systemic exposure due to the low body weight may not raise any safety concern.*

Abbreviated review for *in vivo* release rate calculation

Reference ID: 3226051

Background:
Using an IVIVC model, the *in vivo* release rate of LCS12 was calculated to be (b) (4) The average release over the entire period of 3 years is about (b) (4) Per Biopharmaceutics reviewer Dr. Sandra Suarez Sharp, the proposed IVIVC model failed to adequately predict the LNG *in vivo* release for the first three months after insertion. Therefore, the Agency requested the Sponsor calculate the *in vivo* drug release based on observed values. The Sponsor submitted the response to the information request on July 25th 2012, which calculated the *in vivo* release rate based on ex vivo residual content data for LCS12 observed in Phase 3 study A52238 using NonMEM.

Objectives
To estimate the *in vivo* release rate:

- in the early phase: on day 25 (i.e., 24 days after insertion)
- after two months: release rate at 60 days after insertion
- at the end of treatment: release rate at 3 years after insertion
- average release rate from insertion until 3 years after insertion

Data
The same dataset as for the model in the population PK evaluation of the study A52238 was used. The model for the *in vivo* release from LCS12 was developed based only on the observed ex vivo residual content data for LCS12 in this dataset. The subset from the dataset considered here included 763 subjects with a total of 763 LCS12 residual content measurements for study A52238.

Method
The data were analyzed using NONMEM, version 7.2.0 together with R, version 2.15.0 for goodness of fit assessment. Release rates were then calculated using the software R based on the model developed in NONMEM.

The model includes a zero-order release as first release and a first-order release with time-dependent release rate as second release:

- $release1(t) = C12,$
- $release2(t) = C13 \cdot LNGLCS12(t)/(T1+ t),$
- $d/dt\ LNGLCS12(t) = -release1(t) - release2(t),$

where C12 denotes the first release rate and C13 the second release rate, LNGLCS12 the amount of LNG in the IUS for LCS12, t the time and the parameter T1 regulates the time dependency.Inclusion of the parameter T1 helped improve the model as diagnostic plots suggested.

Results
The parameter estimates of the release model are listed in Table 1. A comparison of the observed and the predicted cumulative release is shown in **Figure 1**. The observed cumulative release was calculated by residual content (i.e., initial content – residual content). (b) (4)

.

Table 1 Parameter estimates together with standard errors and confidence intervals of the release model for LCS12

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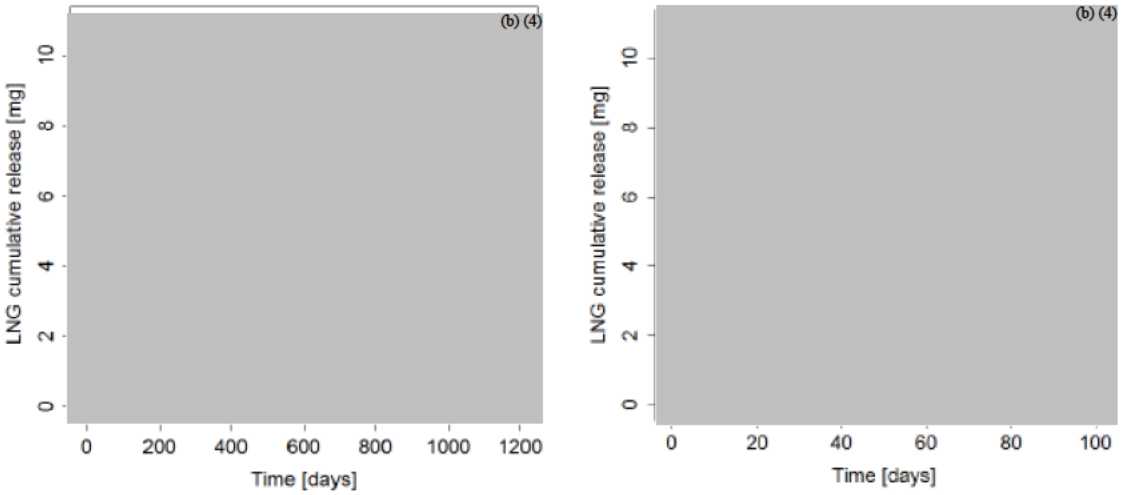
Parameter	Unit	Estimate	RSE [%][a]	LLCI[b]	ULCI[c]	Description
Fixed effects						
C12	ng/h	(b) (4)				
C13	-					
T1	h					
Random effects						
Residual error[d]						
(b) (4)	%					
LCS12 content						

a RSE = relative standard error, expressed as percentage of estimate
b LLCI = lower limit of the 95% confidence interval (estimation – 1.96 x standard deviation)
c ULCI = upper limit of the 95% confidence interval (estimation + 1.96 x standard deviation)
d the coefficient of variation (CV) is calculated here by an approximation (first-order Taylor expansion) which is the square root of the variance

Figure 1 Cumulative observed and predicted release for LCS12



Abbreviated review study A229 Pharmacokinetics of the iv and oral Administration of LNG

Objective:

Reference ID: 3226051

- To evaluate the absolute bioavailability of LNG after oral administration compared to an iv injection
- To investigate dose linearity of oral LNG administration

Reviewer's note: The review will be focused on the i.v. administration route and the determination of half-life of LNG after i.v. administration.

Method:
The open-labeled, randomized cross-over study was performed in 18 healthy young Caucasian women. All subjects received 0.09 mg LNG i.v. and additionally 3 different oral LNG doses (0.03 mg, 0.09 mg and 0.27 mg). Blood (7mL) was drawn at 5 minutes, 10 minutes, 15 minutes, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12 hours after drug administration.

Results:
Pharmacokinetics after i.v. administration: The highest mean serum concentration of LNG (4.62 ±1.39 ng/mL) was observed at the first sampling time (5 minutes after dosing). Thereafter, mean serum levels declined in three phases to 0.11 ± 0.08 and 0.03 ± 0.04 ng/mL at 48 and 72 hours after dosing, respectively.
The individual serum level-time courses were evaluated both, model-independently and with an open three-compartment disposition mode. The results from both approaches of evaluation are summarized in the following table. LNG was eliminated from serum with a half-life of about 20 hours, total clearance amounted to 1 mL/min/kg, AUC (area under the drug concentration vs time curve from time 0 to infinity) to 26 ng·h/mL. The mean residence time (MRT) (of disposition) was calculated at 23 hours, the apparent volume of distribution during the terminal disposition phase (Vz) at 106 L. For Vss, mean values of 85 and 88 L, respectively, were obtained by the model-independent and the compartmental approach.

Table 1: LNG pharmacokinetics after iv administration of 0.09 mg LNG (data is given as mean values ± standard deviation (SD)

Parameter	Unit	Non-compartmental evaluation			Three-compartmental model		
		Mean	SD	Range	Mean	SD	Range
$t_{1/2\lambda 1}$	h	n.c.	n.c.	n.c.	0.12	0.13	0.05 – 0.51
$t_{1/2\lambda 2}$	h	n.c.	n.c.	n.c.	1.25	0.34	0.89 – 2.39
$t_{1/2\lambda z}$	h	19.8	4.4	10.8 – 27.3	20.4	4.1	11.7 – 26.1
AUC(0-t_{last})	ng·h/mL	20.9	8.3	5.1 – 32.9	n.c.	n.c.	n.c.
AUC	ng·h/mL	26.0	7.2	14.4 – 36.6	25.6	7.1	14.1 – 35.3
MRT_{disp}	h	23.1	5.1	13.2 – 32.6	23.5	4.7	13.8 – 30.8
Clearance	mL/min/kg	1.0	0.3	0.7 – 1.7	1.1	0.3	0.7 – 1.8
V_z	L	106.4	37.5	48.2 – 175.7	n.c.	n.c.	n.c.
V_{ss}	L	85.3	27.2	40.5 – 133.1	88.3	26.7	43.0 – 138.3

n.c. = not calculated

Reviewer's comment: *The study design and data analysis are acceptable.*

Abbreviated review for in vitro studies

Study A02495: **In vitro metabolic studies of levonorgestrel (LNG) with human liver microsomes**

Reference ID: 3226051

Objective:

- Identify cytochrome P450 (CYP) isoforms involved in LNG metabolism
- Determine the inhibition potential of LNG on CYP enzymes activities

Method:

- Cytochrome P450 (CYP) isoforms involved in LNG metabolism

Two methods were used to investigate the involvement of CYP1A2, 2A6, 2C9, 2C19, 2D6, 2E1, and 3A4/5 in LNG metabolism.

  - Specific chemical inhibitors of CYP enzymes

Isozyme specific chemical inhibitors were pre-incubated for 15 minutes followed by the addition of a mixture of unlabeled and 14C-labeled LNG at different concentrations (**Table 1**). The decrease of the sum of the high performance liquid chromatography (HPLC) peak areas of the metabolites in the radiochromatogram expressed as % of chromatogram compared to control (complete assay without inhibitor) was used to quantify the extent of inhibition caused by the individual inhibitor.

  - CYP isozymes expressing CYP 3A4, CYP2D6, CYP2C9 and CYP2C19

14C-LNG was pre-incubated followed by initiation of the reaction with the addition of the enzyme preparation. Metabolism of LNG was estimated by alterations in HPLC peak.

Table 1: Inhibitors and concentrations to identify the CYP isoforms involved in LNG metabolism

Inhibitor	Inhibited CYP	Concentration (µM)		
		Conc 1	Conc 2	Conc 3
Furafylline (Fura)	1A2	1	5	25
Pilocarpine (Pilo)	2A6	1	5	25
Sulfaphenazole (Sulf)	2C9	1	5	25
Tranylcypromine (Tran)	2C19	5	25	100
Quinidine (Quin)	2D6	0.4	2	10
Diethyldithiocarbamate (DDC)	2E1	1	5	25
Troleandomycine (TAO)	3A4	4	20	100
Ketoconazole (Keto)	3A4	0.1	0.5	2.5

- Inhibitory effect of LNG on CYP enzymes activities

The inhibitory effect of LNG on the primary CYP isozymes was investigated using human liver microsomes. LNG was pre-incubated at different concentrations (0-250 µM) with microsomes for 15 minutes followed by addition of the model substrate. The inhibition potential was determined by Radio-HPLC measuring the decrease of metabolite formation compared to control (without LNG). The IC50 value of LNG was determined for each CYP isozyme using respective model substrates.

Results:

- Cytochrome P450 (CYP) isoforms involved in LNG metabolism

Figure 1 presented the effects of different chemical inhibitors on the metabolism of LNG following incubation for 30 and 120 minutes. Based on these results, LNG was mainly metabolized by CYP3A4. It should be noted that a concentration dependent decrease in metabolite formation was observed in the presence of tranylcypromine (CYP2C19 inhibitor). However, significant inhibition was only observed at the highest concentration of 100 Mm which is likely to affect also other CYP isozymes due to loss of specificity. From the results of incubation of the test substance with heterologically expressed isozymes, only the CYP3A4 preparation catalyzed the metabolism of LNG (**Table 2**).

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- Inhibitory effect of LNG on CYP enzymes activities

LNG inhibited metabolism of testosterone, a substrate of CYP3A4 (IC50: 18.2-13.6 µM). In addition, LNG did not affect the metabolism of the other model substrates of CYP1A2, 2A6, 2C9, 2C19, 2D6 and 2E1 *in vitro* (**Table 3**).

Considering that C_{max} value of LNG from LCS12 was about four orders of magnitude lower than the determined IC_{50} value, LNG is unlikely to affect the metabolism of other drugs by inhibiting CYP3A4/5 activity.

Figure 1 Effects of chemical inhibitors on the metabolism of LNG following incubation for 30 (A) and 120 (B) minutes with human liver microsomes

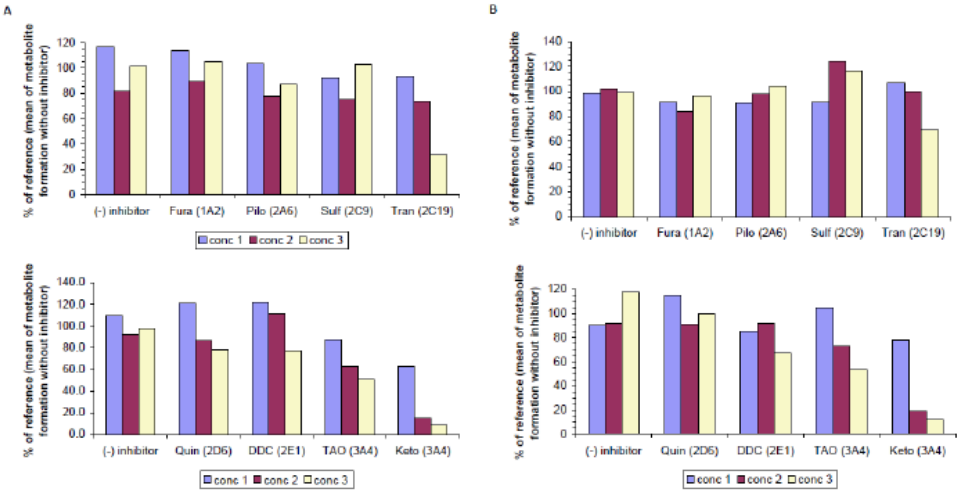

Table 2: Formation of metabolites [% of chromatogram] following incubation of LNG with CYP isoenzymes

Isozyme	LNG µM	Protein conc. mg/ml	Incub. time min	M1	M2	M3	M4	M5	M6	M7	M8	M9	M10	M11	M12	M13	M total	LNG
Human liver microsome	30	0.5	120	-	3.4	1.91	3.09	4.28	4.97	4.25	10.92	9.1	2.91	-	3.03	-	46.8	53.2
Human CYP3A4	50	0.5	60	-	-	-	-	1.4	-	-	2.78	1.4	-	-	-	-	5.58	94.43
Human CYP2C9	200	1	120	-	-	-	-	-	-	-	-	-	-	-	-	-	-	100
Human CYP2C19	50	1	120	-	-	-	-	-	-	-	-	-	-	-	-	-	-	100
Human CYP2D6	50	0.5	60	-	-	-	-	-	-	-	-	-	-	-	-	-	-	100

Table 3: Effect of LNG on metabolism of different model substrates with human liver microsomes

Model substrate	Conc.(µM)	CYP	Incubation time (min)	IC_{50}(µM)
Methoxyresorufin	1	1A2	-	>250
Coumarin	50	2A6	5	>250
Coumarin	50	2A6	20	>250
Tolbutamide	2.00	2C9	40	>250
Tolbutamide	2.00	2C9	120	>250
S-Mephenytoin	50	2C19	40	>250
S-Mephenytoin	50	2C19	120	>250
Dextromethorphan	20	2D6	20	>250
Dextromethorphan	20	2D6	60	>250

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Chlorzoxazone	50	2E1	2D	>250
Chlorzoxazone	50	2E1	60	>250
Testosterone	50	3A4	20	18.2
Testosterone	50	3A4	60	13.6

LNG concentration range: 2.5 ~250 µM

Study A36505: **Calculation of LNG protein binding according to a mathematical model**

Objective

Evaluate a mathematical method to estimate the unbound fraction (f_u) as a function of total drug and protein concentrations and the corresponding dissociation constants (K_D).

Method

The binding of model substrates including gestodene, LNG, and an experimental compound (b) (4) to SHBG and albumin was calculated and compared with experimental data. Based on that, the free concentrations of each substance were calculated. The dissociation constant (K_D) for the albumin-complex were determined experimentally. For SHBG, the experimental determination was not precise enough due to high unspecific binding of the low protein concentrations towards the ultrafiltration device. Therefore, the K_D values for SHBG were derived by curve fitting from published protein binding data. The fraction unbound was then calculated based on the total drug and protein concentrations and the respective K_D values

Results

For all 3 compounds the calculated and experimental free fractions decreased with increasing SHBG-concentration and the mean experimental data were in good agreement with the simulations. Actual albumin concentrations in the plasma samples were of minor importance for the calculated free fractions. Due to the high variability in the experimental data, the simulations under- or over-predicted some individual data.

Conclusions

The presented method was able to predict the mean unbound drug fraction satisfactorily and reproduced the expected effect of an elevated or lowered concentration of high affinity-binding proteins on the free fraction f_u.

Physiologically-based pharmacokinetic modeling (PBPK) and Simulation Review Memo

Ping Zhao, Ph.D., Office of Clinical Pharmacology

Reference ID: 3226051

Reviewed by Shiew Mei Huang, Ph.D., Deputy Director, Office of Clinical Pharmacology

NDA number:	203159
Drug Name:	Levonorgestrel
Sponsor:	Bayer Healthcare
OCP Reviewer:	Li Li, Ph.D.
PBPK consult requested by:	Li Li, Ph.D.
OCP Team Leader:	Myong-Jin Kim, Ph.D
OCP Division:	**Division of Clinical Pharmacology 3**

Reference ID: 3226051

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1. RECOMMENDATIONS

Specific drug elimination pathways should be defined for levonorgestrel (LNG) in the PBPK model. The sponsor should use results of the ongoing adolescent study to refine and update the PBPK model.

2. OBJECTIVES

The objective of this clinical pharmacology review memo is to review study report titled "PBPK study-Pediatric Scaling Levonorgestrel LCS IUD" (Reference 1).

3. SUMMARY OF THE SUBMISSION

LCS12 is one of the levonorgestrel (LNG) intrauterine delivery systems for contraception. The market available LNG intrauterine delivery system, Mirena, was approved more than 20 years ago. In comparison to Mirena, LCS12 is a novel LNG intrauterine delivery system with a smaller T-frame, a lower daily release rate of LNG, and a shorter duration of use (up to 3 rather than 5 years) (Reference 2).

A physiologically-based pharmacokinetic (PBPK) study report (Reference 1) was included in the original NDA. The report described the use of PBPK tools PK-Sim® and MoBi® (versions 4.1 and 2.1, respectively, Bayer Technology Services, Leverkusen, Germany) to investigate pharmacokinetics (PK) of LNG when LCS12 is used in female adolescent of various age groups. In Jan 2012 and Jul 2012, the Office of Clinical Pharmacology at FDA (OCP) requested additional information from the sponsor regarding the purpose of the PBPK modeling work, PBPK software files, and clarification on drug- and system-dependent parameters used in the model.

3.1. Objective of the PBPK modeling and simulation of LCS12

The objective of the PBPK work was provided by the sponsor as a result of FDA information request (Reference 3). Sponsor stated that PBPK model was developed in response to Pediatric Committee (PDCO) in 2009 for the Pediatric Plan of this product, and PDCO considered that the model "to be the most appropriate approach to predict serum concentrations of LNG in adolescent girls (from menarche to the age of 18)." The sponsor performed simulation in10 years old age group to cover a worst-case scenario (described in Reference 1). In addition, the sponsor indicated that "PDCO was satisfied by these simulations and allowed Bayer to start the proposed clinical study with the additional request that Bayer confirm the simulated PK data by means of sparse blood sampling followed by LNG and SHBG analysis in serum and subsequent population pharmacokinetic analysis of these data. The Clinical study in adolescents (Protocol 14371) is ongoing".

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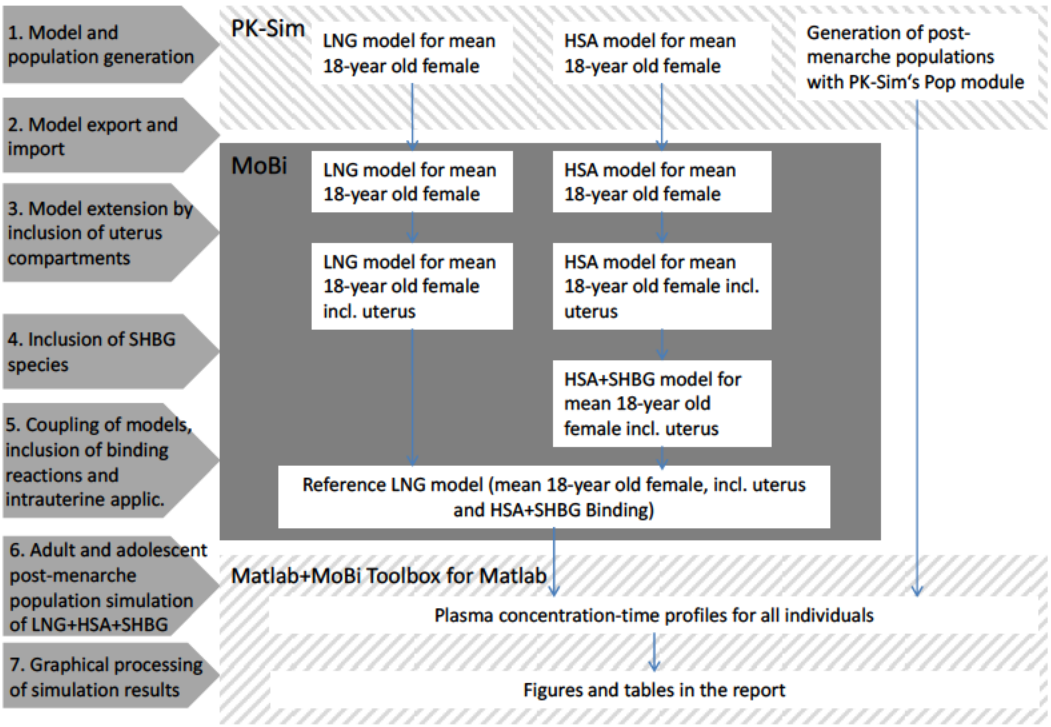
3.2. Workflow of the PBPK modeling of LCS12

As part of the information request, the sponsor provided a PBPK workflow (Reference 4) for the model development, verification, and application process (Figure 1).

Figure 1: Workflow of PBPK modeling and simulation to predict LNG PK in adolescent women using LCS12 (Reference 4)



Abbreviations: LNG, levonorgestrel, HSA, human serum albumin; SHBG, sex hormone binding globulin

The PBPK model of LNG was based on the following assumptions for scaling to female, post-menarche adolescents (Reference 1):

- Variability of the processes governing the PK in adolescents is similar to that observed in adults in particular hepatic clearance
- The percent contribution of the different clearance pathways to the total clearance in adolescents is the same as in adults
- In post menarche adolescents, no further distribution or clearance processes than those observed in adults are assumed

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- SHBG levels and variance in post menarche population is comparable to the observed levels and variance in adults

Drug dependent parameters include physicochemical, hepatic clearance, binding to sex hormone binding globulin (SHBG), in vitro release kinetics of LNG from the intrauterine delivery system, and human single dose PK after intravenous (IV) dosing. Supplemental Table A1 summarizes key drug dependent parameters, along with content of HSA used in the model. Specific clearance of LNG (unit in L/min/liver intracellular volume) was kept the same for adult and adolescent women, and total clearance was then determined by the difference in liver volume. System dependent parameters include standard human physiology data and ontogeny in virtual young female adolescent subjects, which have been incorporated in the software tools. A uterus organ was developed using multiple compartments, including myometrium, basal and functional endometrium, and cavity, and was incorporated in the PBPK models for both LNG and SHBG (Figure 2). Parameters for uterus model are summarized in Appendix Table A2.

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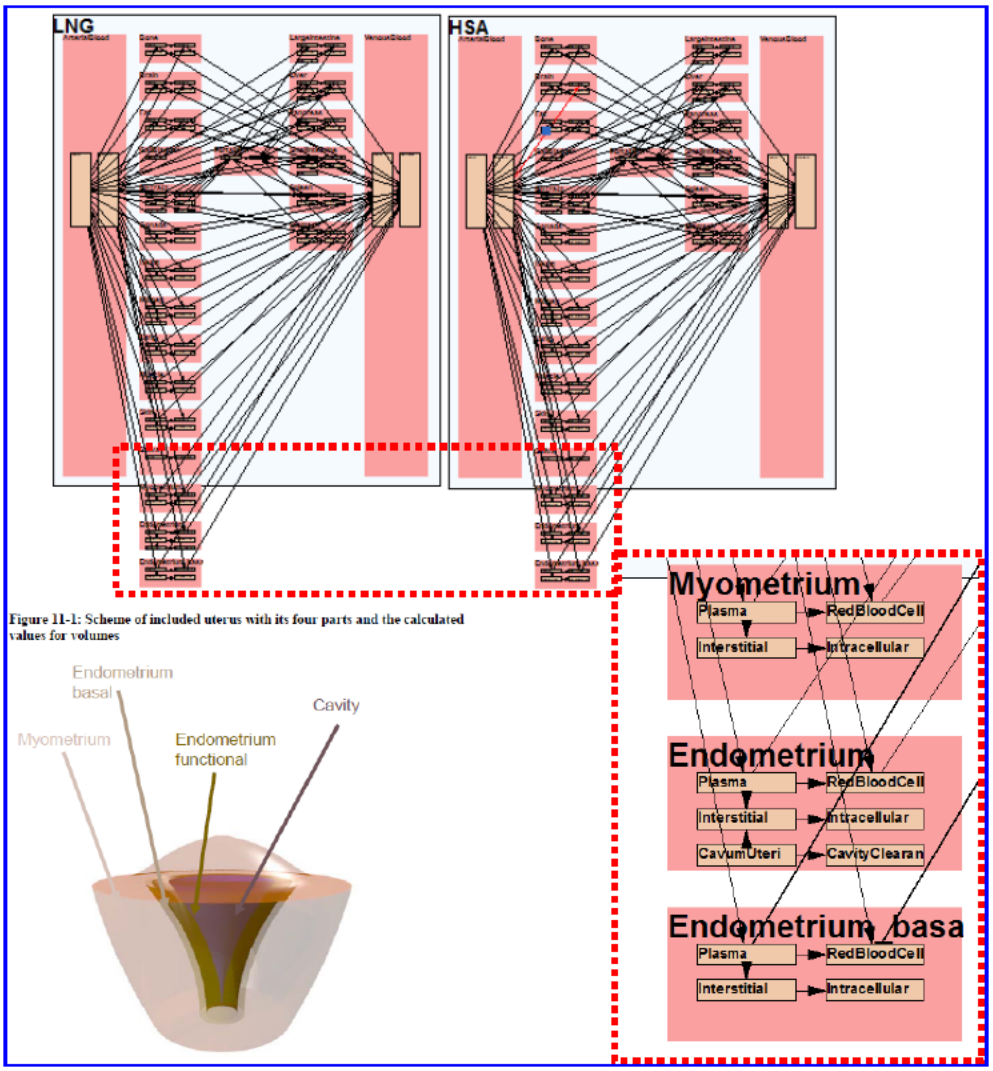
Figure 2. Representation of uterus in the PBPK model for LNG and SHBG (PBPK model schemes from submitted MoBi file and cartoon of uterus from Figure 11-1 of Reference 1)



3.3. Model performance and verification measured by plasma LNG pharmacokinetics

The observed LNG plasma concentration-time data after IV dosing of LNG were compared to the simulated mean plasma PK profile using the final PBPK model of LNG (Figure 3, left panel). Verification of the PBPK model was accomplished by comparing LNG plasma PK data in subjects taking oral LNG (Figure 3, right panel) or using either LNS12 or LNS16 (another LNG intrauterine delivery system) (Figure 4).

Figure 3. Comparison of simulated LNG plasma concentration-time profiles with observed data after

single dose intravenous (left) and oral (right) administration of LNG in humans (Figure 12-1 and 12-2 from Reference 1)

Figure 12-1 : Predicted mean vs. observed individual plasma PK profiles (x = data points) for adult females following IV administration of 0.09 mg Levonorgestrel (Data taken from study A229). Close-up view of time range 0 to 4 h inserted on top right side.

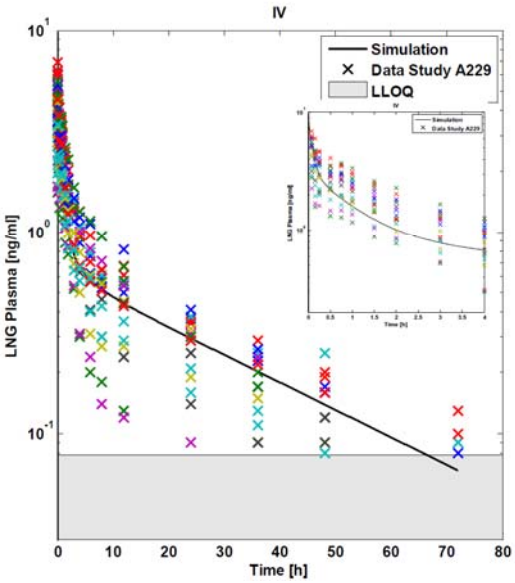


Figure 12-2: Predicted mean vs. observed individual plasma PK profiles (x = data points) for adult females following PO administration of 0.09 mg Levonorgestrel (Data taken from study A229). Close-up view of time range 0 to 4 h inserted on top right side.

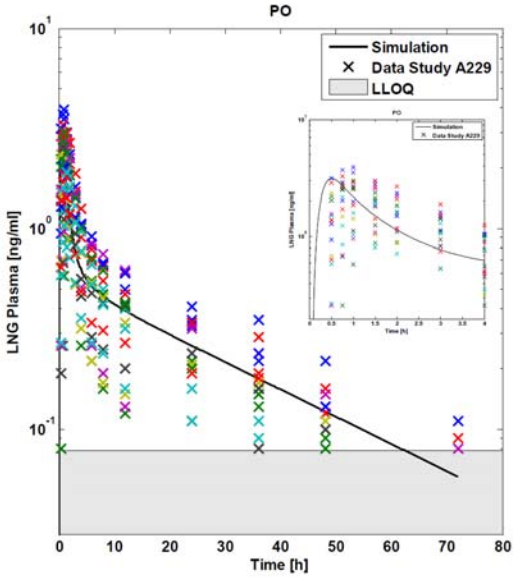


Figure 4. Comparison of LNG plasma concentration-time profiles simulated using PBPK model with observed data in adults using LNG intrauterine delivery systems (Figure 12-3 and 12-4 from Reference 1)

Figure 12-3: Predicted mean vs. observed individual plasma PK profiles (x = data points) for adult females following LCS12 IUD administration (Data taken from study 308901). Close-up view of time range 0 to 14 h inserted on bottom left side.

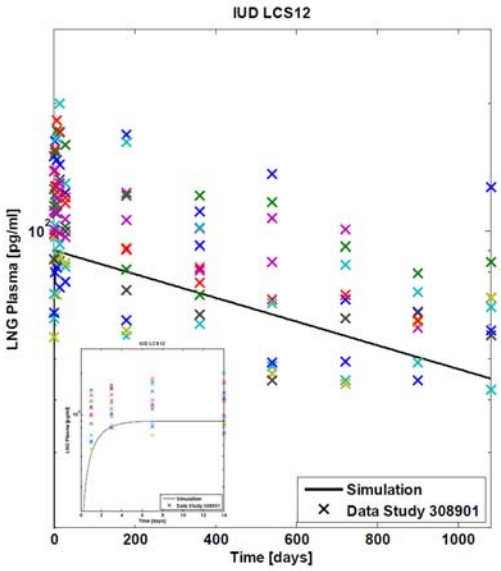
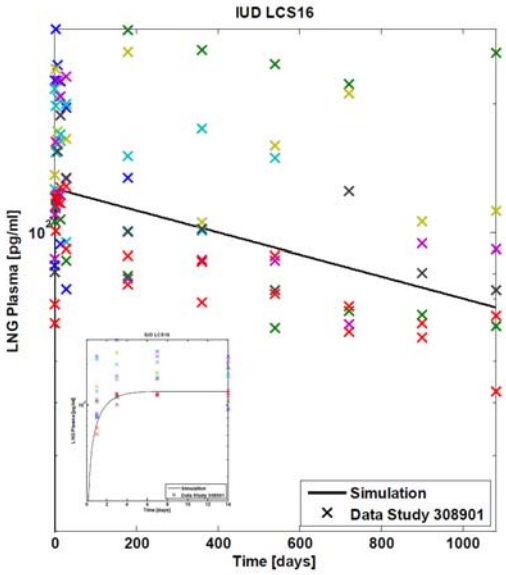


Figure 12-4: Predicted mean vs. observed individual plasma PK profiles (x = data points) for adult females following LCS16 IUD administration (Data taken from study 308901). Close-up view of time range 0 to 14 h inserted on bottom left side.



3.4. Model application – predicting LNG plasma clearance in adolescent women

Figure 5 shows the simulated age-dependence of specific intrinsic hepatic CL in units of L/min for female adolescents. Simulations of plasma LCS PK were made in virtual female adolescents (10-18 years) using LCS12.

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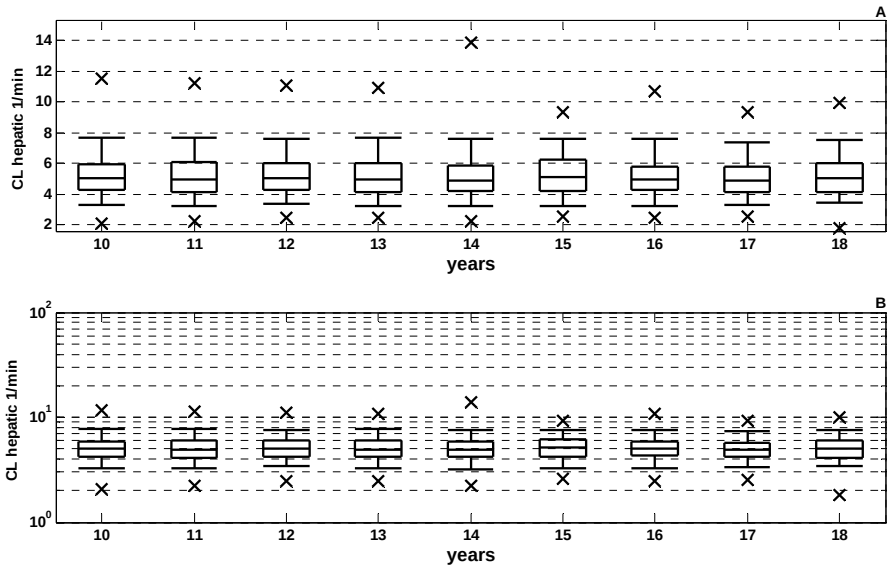
Figure 5. Simulated hepatic clearance of LNG as a function of age in adolescent women (Graph (A) linear, and (B) semi-log representations; Figure 13-4 of Reference 1)



4. QUESTION-BASED REVIEW

4.1. Dose the PBPK model of LNG sufficiently describe the plasma PK of LNG in adult females using LCS12?

Yes, the PBPK model sufficiently described plasma PK of LNG in adult females after IV, PO, and the use of LCS12.

4.2. Is the PBPK model of LNG developed using adult data able to predict plasma PK of adolescent women taking LCS12 LCS-IUD?

The PBPK model of LNG developed and verified in adult female offered a mechanistic basis for the prediction of plasma LNG PK in adolescents taking LCS12 LCS-IUD. Physiological differences have been incorporated in the model structure.

The submitted PBPK model has limitation with regard to LNG clearance. The sponsor assumed that hepatic metabolism was the only route of LNG elimination. This assumption may be satisfactory for size-based extrapolation (see assumptions above in 3.2) of drug disposition pathway for older pediatric groups. Levonorgestrel is reported to be metabolized by CYP3A4 enzyme, and unchanged LNG was found in the

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urine, suggesting possible renal elimination of the drug (LNG drug label). For broader application of the PBPK model, detailed drug disposition mechanisms need to be considered in the model.

5. SUMMARY

The submitted PBPK model of LNG appears to adequately describe LNG plasma PK in female adults using IV LNG, PO LNG, or LCS12. The model can be used to predict LNG plasma PK in adolescent females taking LCS12. For broader application of the model, specific drug elimination pathways should be defined for LNG in the PBPK model. The sponsor should use results of the ongoing adolescent study to refine and update the PBPK model.

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6. REFERENCES

1. Bayer Healthcare: Modeling and Simulation Report No. A57120 “PBPK study-Pediatric Scaling Levonorgestrel IUD”

2. Bayer Healthcare: NDA203159 “Summary of Clinical Pharmacology Studies”

3. Bayer Healthcare: NDA203159 “NDA203159 [eCTD Sequence No.0011] LCS12 (levonorgestrel-releasing intrauterine system) 13.5 mg Other: Response to FDA Information Request re: Clinical Pharmacology”, in response to FDA’s information request

3. Bayer Healthcare: NDA203159 “How to handle the submitted electronic information”, Microsoft word document (Supportive Documententaion.doc) submitted per OCP information request on July 2, 2012

4. Bayer Healthcare: Report A36505 “Evaluation of a Evaluation of a mathematical method for estimating the fraction of unbound drug in plasma (fu) as a function of total drug concentration and the concentration of two main binding partners”

5. Bayer Healthcare: Report A36505 “Evaluation of a mathematical method for estimating the fraction of unbound drug in plasma (fu) as a function of total drug concentration and the concentration of two main binding partners”

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7. APPENDIX

Table A1: Summary of drug-dependent parameter

Parameter	Value (Unit)	Source and comments
LNG		
Molecular weight	312.44 (g/mol)	
Log P	2.8	Optimized using iv data; Reference 1
Unbound fraction in plasma fu	1.0	In both final PK-Sim and MoBi file for LNG
Oral absorption	Fa =1	According to final PK-Sim file for LNG; no gut metabolism was assumed in final Mobi file
Volume of distribution	Not reported	According to final PK-Sim file for LNG, using Log P of 2.8, software built-in PK-Sim Standard method calculated 184 L/kg
Hepatic specific clearance	4.99 (L/min)	The only route of drug elimination from final MoBi file. The term operates on liver intracellular drug concentration
Renal clearance	0	No renal elimination in Final PK-Sim and MoBi file for LNG
HSA		
Molecular weight	67000 (g/mol)	Reference 1
Log P	3.0	Reference 1
LNG binding to HSA		
K_on	6.5 (/min)	Reference 1
Kd	19.3612 (/uM)	Reference 1
LNG binding to SHBG		
K_on	17.4 (/min)	fitted
Kd	0.0012 (/uM)	Reference 1
Calculated release rate		
From LCS 12	8.71*e^(-0.0007098t)	Ex vivo determination, and t is days after insertion

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From LCS 16	12.58*e^(-0.0007098t)	Ex vivo determination, and t is days after insertion

Table A2: System dependent parameters for uterus in PBPK model

Table 11-1: Uterus volumes, tissue composition and blood flows

Organ/Parameter	Value
Myometrium	
Volume	42.6 cm^3 [a]
Tissue fractions	
Vascular fraction	0.024 [b]
Interstitial fraction	0.094 [b]
Intracellular fraction	0.882 [b]
Tissue Composition (fractions)	
Water	0.831 [c]
Lipids	0.04 [d]
Proteins	0.163 [c]
Blood flow	38.85 ml/min [f]
Endometrium (basal)	
Volume	2.270 cm^3 [a]
Tissue fractions	
Vascular fraction	0.048 [e]
Interstitial fraction	0.188 [e]
Intracellular fraction	0.764 [e]
Tissue Composition (fractions)	
Water	0.827 [e]
Lipids	0.017 [e]
Proteins	0.1175 [e]
Blood flow	1.94 ml/min [f]
Endometrium (functional)	
Volume	3.628 cm^3 [a]
Tissue fractions	
Vascular fraction	0.048 [e]
Interstitial fraction	0.188 [e]
Intracellular fraction	0.764 [e]
Tissue Composition (fractions)	
Water	0.827 [e]
Lipids	0.017 [e]
Proteins	0.1175 [e]
Blood flow	32.46 ml/min [f]
Uterine cavity	
Volume	2.379 cm^3 [a]
Tissue Composition (fractions)	
Water	1.0
Lipids	0.0
Proteins	0.0

a Calculated from thicknesses of functional layer, blood flows, vascular volumes scaled corresponding to thicknesses (29, 35-37).
b Myometrial tissue fractions was adopted from similar tissue with smooth muscle, i.e. large intestine (26).
c Cheek et al. 1985 (27).
d Pulkkinnen et al. 1996 (31).
e ICRP(15).
f Calculated from a Doppler-Sonography Study (29, 35).

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4.2 NDA Filing and Review Form

NDA Number: 203159 **Applicant:** Bayer HealthCare Pharmaceuticals Inc. **Stamp Date:** 12/09/2011

Drug Name: LCS12 (Skyla™, low-dose levonorgestrel intra-uterine delivery system) **NDA Type:** Original

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			x	
2	Has the applicant provided metabolism and drug-drug interaction information?	x			
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	x			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	x			
5	Has a rationale for dose selection been submitted?	x			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	x			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	x			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	x			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	x			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			x	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	x			
12	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)?	x			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			x	
14	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?			x	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			x	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?	x			

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17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	x			
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	x			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			x	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
___Yes___

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

- Your report "PBPK study-Pediatric Scaling Levonorgestrel LCS IUD" includes simulations from a PBPK model. To facilitate the review of this report we request that you submit the PK-Sim project files and specifically describe how the following drug dependent and system dependent information have been incorporated in the PK-Sim software:
  - Uterus compartment
  - SHBG protein
  - Release characteristics of the active components from the IUD
  - Any additional customization

  The project files should be executable using PK-Sim version 4.2, and should include both initial structural model and final structural model after optimization of initial input parameters using human PK data.
- **Internal Comment**: Per our internal discussion, the ONDQA Biopharm review team will be sending an information request to the Sponsor to present the *in vitro/in vivo* correlation (IVIVC) data and *in vitro* dissolution data in an adequate fashion to bridge formulation changes from Phase 2 to Phase 3 and from Phase 3 to the To-Be Marketed (TBM) product, respectively.

Review Issue:
We note that you propose to utilize the absorption data derived from Population PK analysis in the product label. This will be a review issue.

Li Li	02/06/2012
Reviewing Clinical Pharmacologist	Date
Chongwoo Yu	02/06/2012
Team Leader/Supervisor	Date

Reference ID: 3226051

Filing Memo

Clinical Pharmacology Review

NDA: **203159**

Compound: **LCS12 (Skyla™): a low-dose levonorgestrel (LNG) intra-uterine delivery (IUD) system**

Sponsor: **Bayer HealthCare Pharmaceuticals Inc.**

Date: **01/10/2012**

Reviewer: **Li Li, Ph.D.**

Introduction:
Bayer HealthCare Pharmaceutical submitted a New Drug Application (NDA) for LCS12 (Skyla™), a low-dose LNG IUD system on December 9, 2011 for the indication of prevention of pregnancy. Worldwide, there is currently no marketing authorization for LCS12. Mirena®, the only LNG-IUD currently on the market, was approved in the US on December 6, 2000 under NDA 021225. In comparison to Mirena®, LCS12 has a smaller T-frame, a lower daily release rate of LNG, and a shorter duration of use (up to 3 years rather than 5 years). A silver ring is added around the vertical stem of the T-frame to facilitate detection during ultrasound examination. Additionally, the insertion tube diameter for LCS12 is smaller than that of Mirena® and the Sponsor believes this will result in an easier and less painful insertion procedure, particularly in young and nulliparous women. The proposed proprietary name for LCS12 to be marketed in the US is Skyla™.

To establish the safety and efficacy of LCS12, a pivotal Phase 3 study (A52238) and a supporting Phase 2 clinical study (A46796) evaluating contraceptive efficacy, bleeding patterns, as well as safety parameters were performed between 2005 and 2011. Of the two studies, Phase 2 study A46796, conducted outside of US, was a dose-finding study investigating LCS12 and LCS16 compared to Mirena® for a maximum of 3 years. Per Sponsor, this study indicated that both investigational doses demonstrated similar efficacy and safety, and thus LCS12 would be considered as the lowest safe and effective dose over a 3-year period of treatment. Both LCS12 and LCS16 were selected for further investigation in Phase 3 study A52238 for 3-year period of treatment. The investigation on LCS16 is extended for additional 2 years to explore its potential as a 5-year product. In the Phase 3 study, a total of 1432 women from 18 to 35 years old were

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assigned for LCS12 assessment. The mean Body Mass Index (BMI) was 25.32 kg/m^2 with 17% of study subjects having a BMI over 30 kg/m^2. This trail was conducted in the US under IND 073505.

No clinical pharmacology studies were conducted with LCS12. The pharmacokinetic (PK) characterization of LCS12 is mainly based on the Phase 2 and Phase 3 studies. In both studies, a dense sampling scheme in a subset of 12 women per treatment arm was conducted to determine non-compartmental PK parameters of LNG during LCS12 treatment. In the Phase 3 study, a sparse sampling scheme (one sample/subject) was conducted in all subjects for a population PK analysis. Pharmacodynamic (PD) characteristics including effects on ovulation, cervix, and endometrium, as well as evaluation of serum silver concentrations were investigated in a subset of 20 women per treatment arm in both clinical studies. Additional supporting data include a PK/PD population analysis using data from the 2 studies (A57551 and A57552) mentioned above, a Physiology-based PK (PBPK) analysis comparing the PK of LNG between female adolescents (10-18 years old) and adults following LCS12 insertion (A57120), one *in vitro* study determining LNG protein binding (A36505) and one *in vitro* study identifying cytochrome P450 (CYP) isoenzymes involved in LNG metabolism (A02495). In addition, the Sponsor also submitted two *in vivo* supplementary studies, i.e., Study A229 characterizing the PK of LNG following intravenous (i.v.) and oral administration, and Study A10982 describing the course of LNG concentrations at early times after Mirena® insertion and after Mirena® removal. The detailed information for submitted clinical pharmacology studies is summarized in **Table 1**.

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Table 1 Summary of Clinical Pharmacology Studies

Study No.	Study Design/Description	Main objectives regarding to PK/PD parameters
A46796 (Phase 2, Europe)	Multicenter, randomized, open, controlled, 3-arm (LCS12, LCS16, and Mirena®), parallel group for 3 years	• PD - Ovarian, cervical function and hormone concentrations (N = 20/arm, approximately) - endometrial histology (N = 30/arm) • PK of LNG and SHBG (N = 12/ arm)
A52238 (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 = 20/arm, approximately) - endometrial histology (N = 30/arm) • PK of LNG and SHBG, Serum silver ion concentration (N = 12/ arm)
A57551	Development of population PK model	Development of a population PK model based on phase 2 data for the description of LNG PK in serum
A57552	Population PK Evaluation of Phase 3	• Application of the developed population PK model • Estimation of LNG serum concentrations over the 3 years of use of LCS12 • Investigations on the impact of body weight and other covariates
A57120	PBPK study – Pediatric Scaling	Development of a physiologically based PK model to predict the PK of LNG in adolescents after application of LCS
A36505	Calculation of LNG protein binding according to a mathematical model	LNG protein binding (model) to predict free fraction of LNG
A02495	*In vitro* study: drug interaction and metabolism study	• CYP isozymes involved in LNG metabolism and enzyme kinetics of LNG • Inhibitory effect of LNG on metabolism of CYP isozymes
A229	Single center, randomized, open, single dose, cross-over	• PK parameters (i.v. treatment) • dose linearity of the oral drug product
A10982	Multicenter, open, non-randomized for 1 year	PK of LNG after Mirena® insertion and removal

Drug Product Formulation:

Phase 2 Formulation vs Phase 3 Formulation

The formulations of LCS12 used in the Phase 2 and Phase 3 clinical studies were slightly different. (b) (4) . The other changes from the Phase 2 to the Phase 3 formulations were the addition of a silver profile (ring) and some modifications in the design of the T-body. Per ONDQA reviewer Dr. Sandra Suarez, a bridging for the formulation change can be supported by the submitted *in vitro/in vivo* correlation (IVIVC) model and *in vitro* dissolution data. The ONDQA will request the Sponsor to submit the data in an adequate fashion for bridging.

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

Compared to the product used in Phase 3 study, minor modifications have been implemented for the TBM product, namely, the removal threads, the modified inserter and further minor modifications of the T-body. Per ONDQA reviewer Dr. Sandra Suarez, based on the level of changes in the TBM product, a bridging study is needed and the bridging for the formulation change can be supported by the submitted *in vitro/in vivo* correlation (IVIVC) model and *in vitro* dissolution data for both TBM product and the Phase 3 product. The ONDQA will request the Sponsor to submit the data in an adequate fashion for bridging. The clinical and TBM formulations of LCS12 are presented in **Table 2**.

Table 2 The clinical and TBM formulations of LCS

Component/description	Phase 2 (#308901)	Phase 3 (#310442, #91775)	Phase 3b (#13362, #13363, #14371) and commercial products
Drug product batch no.	(b) (4)		
Drug (b) (4) Composition (b) (4)			
Membrane (b) (4) (b) (4) Membrane thickness target Material (b) (4)			
T-Body Composition Dimensions Length of horizontal arm × vertical stem × diameter of vertical stem Silver profile			
Removal thread Composition Dimensions			
Inserter Insertion applicator			

Absorption

Release of LNG from the IUD starts immediately after insertion into the uterine cavity. Per Sponsor, the *in vivo* release rate is approximately 10 µg/day in weeks 3-4 and is reduced to approximately 5 µg/day after three years. The maximum serum concentration (C_{max}) of LNG was

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171 ± 89 ng/L (N=7), reached within the first two weeks after insertion of LCS12. Thereafter, the serum concentration of LNG decreased slowly to mean value (C_{ave}) of 70 ± 30 ng/L (N=8).

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. Per Sponsor, the data in Phase 3 study indicated that the concentration of SHBG declined by about 15% within 2 weeks after insertion of LCS12. Thereafter, plateau-like serum levels were observed.

Metabolism

LNG is almost completely metabolized. No pharmacologically active metabolites of LNG have been identified. Most of the metabolites that circulate in the blood are sulfates of 3α, 5β-tetrahydro-LNG, while excretion occurs predominantly in the form of glucuronides. Per Sponsor, i*n vitro* studies have demonstrated that oxidative metabolism of LNG is catalyzed by CYP enzymes, especially CYP3A4.

Excretion:

Following i.v. administration of 0.09 mg LNG to healthy volunteers, the total clearance of LNG from plasma is approximately 1 mL/min/kg and the elimination half-life is approximately 20 hours. Only trace amounts of LNG are excreted in unchanged form. The metabolites are excreted with feces and urine at an excretion ratio of about 1.

Drug-Drug Interactions:

No clinical DDI study was conducted under this NDA. Information from the *in vitro* DDI studies conducted with LNG in the current NDA submission is presented below:

<u>Effects of Other Drugs on LNG</u>

Per Sponsor, *in vitro* studies demonstrated that oxidative metabolism of LNG is mainly metabolized by CYP3A4. Thus, drugs which are affecting the activity of CYP3A4 may change the PK of LNG.

<u>Effects of LNG on other Drugs</u>

Per Sponsor, i*n vitro studies* have shown that LNG is unlikely to affect the metabolism of other drugs by CYP3A4/5, as C_{max} value of LNG from LCS12 is about four orders of magnitude lower than the determined IC_{50} value. In addition, LNG did not affect the metabolism of the other model substrates of CYP1A2, 2A6, 2C9, 2C19, 2D6 and 2E1 *in vitro*.

Specific Populations and Waivers:

- Renal / hepatic impairment: No formal studies have evaluated the effect of renal or hepatic disease on the disposition of LCS12.
- Pediatric Study waiver request: The Sponsor requests a partial waiver for pre-menarche children as they are not at risk of becoming pregnant. The Sponsor requests that the Pediatric Research Equity Act (PREA) requirements for postmenarchal pediatric patients be deemed fulfilled by extrapolation of adult data. The final decision will be made by Pediatric Review Committee (PeRC) during the review cycle.

Bioanalytical Method Validation:

Bioanalytical study reports and validation reports for the following analytes were submitted for review:

- LNG was determined in human serum with a validated radioimmunoassay (RIA) method

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- The concentration of SHBG in human serum was determined with a time-resolved fluoroimmunoassay (TR-FIA)
- Silver was determined in serum by a validated ICP-MS method.

Recommendation:
The Office of Clinical Pharmacology/Division of Clinical Pharmacology 3 finds that the Clinical Pharmacology section for NDA 203159 is fileable.

Office of Clinical Pharmacology

NEW DRUG APPLICATION FILING AND REVIEW FORM

General Information About the Submission

	Information		Information
NDA Number	**203159**	**Brand Name**	**SKYLA™**
OCP Division	**DCP3**	**Generic Name**	**levonorgestrel**
Medical Division	**DRUP**	**Drug Class**	**Hormonal contraceptives**
OCP Reviewer	**Li Li, Ph.D**	**Indication(s)**	**prevention of pregnancy**
OCP Team Leader (acting)	**Chongwoo Yu, Ph. D.**	**Dosage Form**	**intra-uterine delivery system**
Secondary Reviewer	**Chongwoo Yu, Ph. D.**	**Dosing Regimen**	**3 years**
Date of Submission	**Dec. 09, 2011**	**Route of Administration**	**intra-uterine**
Estimated Due Date of OCP Review	**July. 26, 2012**	**Sponsor**	**Bayer Healthcare Pharmaceutical Inc.**
PDUFA Due Date	**Oct. 09, 2012**	**Priority Classification**	**Standard**
Division Due Date			

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	**Number of studies submitted**	**Number of studies reviewed**	**Critical Comments If any**
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:	X	1		A02495
Blood/plasma ratio:				
Plasma protein binding:	X	1		A36505

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Pharmacokinetics (e.g., Phase I) -				
HEALTHY VOLUNTEERS- ***(WOMEN WITH CHILDBEARING POTENTIAL)***				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:	X	1		A229 (supplementary)
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:	X	-		A02495
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:	X	1		A57120
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 1:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:	X	3		A46796 (Phase 2) A52238 (Phase 3) A10982 (Mirena®, supplementary)
Population Analyses -				
PK/PD	X	2		A57551, A57552
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):	X	1		A57411
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				

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Chronopharmacokinetics				
Pediatric development plan				
Immunogenicity profile				
Thorough QT study				
Literature References				
Total Number of Studies		10		

Other comments

	Comments

QBR questions (key issues to be considered)	• PK characterization:
	  o Non-compartmental PK analysis from dense sampling scheme
	  o Population PK analysis from sparse sampling scheme
	• PD characterization: effect of LCS12 treatment on SHBG concentration
	• PBPK analysis: comparison of LNG PK between adult females and adolescent females during LCS 12 treatment
	• Bioanalytical method validation and performance
	• *In vitro* drug interaction study:
	  o CYP isoenzymes involved in LNG metabolism and enzyme kinetics of LNG
	  o Inhibitory effect of LNG on metabolism of CYP isoenzymes

Other comments or information not included above	None

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/s/

LI LI
12/05/2012

PING ZHAO
12/05/2012

MYONG JIN KIM
12/05/2012

BIOPHARMACEUTICS REVIEW Office of New Drug Quality Assessment			
Application No.:	NDA 203-159 (000)	**Reviewer:** Sandra Suarez Sharp, Ph.D.	
Division:	DRUP		
Applicant:	Bayer HealthCare	**Biopharmaceutics Team Leader:** Angelica Dorantes, Ph.D .	
Trade Name:	Skyla	**Biopharmaceutics Lead (acting):** Richard Lostritto, Ph.D.	
Generic Name:	LCS12 (levonorgestrel-releasing intrauterine system) 13.5 mg	**Date Assigned:**	Dec 22, 2011
Indication:	Prevention of pregnancy for up to 3 years	**Date of Review:**	Nov 19, 2012
Formulation/strength	Intrauterine system		
Route of Administration	Intrauterine		

SUBMISSIONS REVIEWED IN THIS DOCUMENT			
Submission date	**CDER Stamp Date**	**Date of informal/Formal Consult**	**PDUFA DATE**
Dec 9, 2011 May 17, 2012 June 27, 2012 July 10, 2012 Sep 27, 2012	Dec 9, 2011	Dec 21, 2011	Oct 9, 2012
Type of Submission:	Original NDA		
Type of Consult:	• Release rate method and acceptance criteria • Data Supporting Manufacturing changes • IVIVC model		

SUMMARY OF BIOPHARMACEUTICS FINDINGS:

Mirena® (Levonorgestrel- releasing intrauterine system; 20 µg/day; in vitro) (Berlex) was approved by the FDA in December 2000 under NDA 21-225 for intrauterine contraception for up to 5 years. Skyla, low Dose Levonorgestrel Contraceptive System (LCS) (12 µg/day; in vitro) is a hormone-elastomer reservoir (b) (4) mounted in a T-shaped polyethylene frame-releasing intrauterine system being proposed by Bayer Healthcare to provide a 3-year contraceptive system that can be inserted more easily and with less discomfort compared to Mirena®.

The Biopharmaceutics review is focused on the evaluation of: 1) The acceptability of the in vitro drug release rate method; 2) The acceptability of the in vitro and in vivo drug release rate specifications; 3) The acceptability of the IVIVC model, and; 4) The information/data supporting the bridging between the formulations used throughout development.

1) In vitro drug release method and acceptance criteria:

The following drug release method and acceptance criteria have been agreed upon with the Applicant (refer to submission dated Sep 27, 2012).

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Dosage Form	Apparatus	Speed	Medium	Volume (mL)	Sampling times	Acceptance criteria
IUR	Bottle/ rotary water-bath (b) (4) Shaker	70 strokes Per min	1.0% 2-ydroxypropyl-β-cyclodextrin (2-HPBCD) dissolution medium at 37 °C.	75 mL	Days 2, 11, and 25	(b) (4) Meets USP <724> L1, L2 or L3 criteria as appropriate

The setting of the acceptance criteria was based on the in vitro performance of the batches tested in the phase 3 clinical trial.

(b) (4)

3) Appropriate bridging between the formulations used throughout development.

Throughout the development the proposed drug product underwent several modifications. The drug product used in Phase 2 differs significantly from that used in the Phase 3a trials. (b) (4) This modification led to re-validation and optimization of the assembly process, (b) (4) These changes are considered major; however, since there is PK information for the new formulation tested in the phase 3a trials and the data from the phase 2 trials are not considered essential for the approval of this NDA, no additional data are needed to bridge these formulations.

Further modifications to the T-body such as removal thread and inclusion of an inserter were implemented to the pivotal phase 3a clinical batch formulation. The ONDQA review team considered that the implemented manufacturing changes are beyond minor changes that do not require BE studies, but needed

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to be supported with dissolution profiles comparison data. During the review cycle, the Applicant provided long term dissolution profiles comparisons demonstrating that the batches tested in the phase 3a and the phase 3b/commercial formulation have similar in vitro drug release (f2 > 50).

RECOMMENDATION:
The ONDQA/Biopharmaceutics team has reviewed original NDA 203-159 submitted on Dec 9, 2011, and its amendments subsequently submitted.

The following drug release method and acceptance criteria have been already agreed upon with the Applicant (refer to submission dated Sep 27, 2012):

Dosage Form	Apparatus	Speed	Medium	Volume (mL)	Sampling times	Acceptance criteria
IUR	Bottle/ rotary water-bath (b) (4) Shaker	70 strokes Per min	1.0% 2-ydroxypropyl-β-cyclodextrin (2-HPBCD) dissolution medium at 37 °C.	75 mL	Days 2, 11, and 25	(b) (4) Meets USP <724> L1, L2 or L3 criteria as appropriate

The setting of the acceptance criteria was based on the in vitro performance of the batches tested in the phase 3 clinical trial.

From the Biopharmaceutics perspective, NDA 203-159 for Low dose levonorgestrel-releasing intrauterine system, 13.5 mg is recommended for approval.

Sandra Suarez Sharp, Ph. D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Angelica Dorantes, Ph.D.
Biopharmaceutics Lead
Office of New Drug Quality Assessment

cc NDA203-159/DARRTS, R. Lostritto

Reference ID: 3221517

BIOPHARMACEUTICS ASSESSMENT

BACKGROUND

Mirena® (Levonorgestrel- releasing intrauterine system; 20 µg/day; in vitro) (Berlex) was approved by the FDA in December 2000 under NDA 21-225 for intrauterine contraception for up to 5 years. Skyla low Dose Levonorgestrel Contraceptive System (LCS) (12 µg/day; in vitro) is a hormone-elastomer reservoir (b) (4) mounted in a T-shaped polyethylene frame-releasing intrauterine system being proposed by Bayer Healthcare to provide a 3-year contraceptive system that can be inserted more easily and with less discomfort compared to Mirena®.

According to the Applicant, the *in vivo* LNG release rate from LCS12 is approximately 10 µg/24 hours in weeks 3 to 4. This rate is reduced to approximately 5 µg/24 hours after three years. The mean release rate of LNG over the period of three years is approximately 6 µg/24 hours.

The Applicant stated that proof of the clinical efficacy of LCS12 is based on a large phase 3 study (A52238, performed in Europe, North and South America) and a phase 2 clinical study (A46796, performed in Europe) conducted between 2005 and 2011. Note that the clinical review team does not consider the phase 2 data to be essential for the approval of this NDA.

REVIEW

The Biopharmaceutics review is focused on the acceptability of the release rate method and acceptance criteria, the acceptability of the IVIVC model and acceptability of the data supporting the bridging between the formulations used throughout development.

BIOPHARMACEUTICS INFORMATION/DATA

Drug Substance

Levonorgestrel

LCG is practically insoluble in water (see table below). The Applicant states that except for the aliphatic hydroxyl-group the LNG molecule does not contain any functional groups, which can be protonated or deprotonated in aqueous solution. LNG is considered to be a neutral molecule with no pKa value in the range of pH 1 – 12.

Solvent	Solubility [mg/ml]	Temperature (°C)	Descriptive Term [a]
Water	0.00105	25	practically insoluble
Buffer pH 1	0.00150	37	
Buffer pH 4.5	0.00147	37	
Buffer pH 6.8	0.00133	37	
Ethanol	4.32	20	slightly soluble
n-Hexane	0.015	20	practically insoluble
Acetone	7.0	20	slightly soluble
Dichloromethane	26.5	20	sparingly soluble

a according to Ph. Eur./USP

Drug Product

Composition

LCS12 consist of a white drug-elastomer core covered with a (b) (4) membrane mounted on the vertical stem of a T-body. The T-body is a white Tshaped

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frame made from polyethylene with a loop at one end of the vertical stem and two arms at the other end. A silver ring is attached to the upper part of the vertical stem of the T-body. Removal threads are attached to the loop (Figure 1).

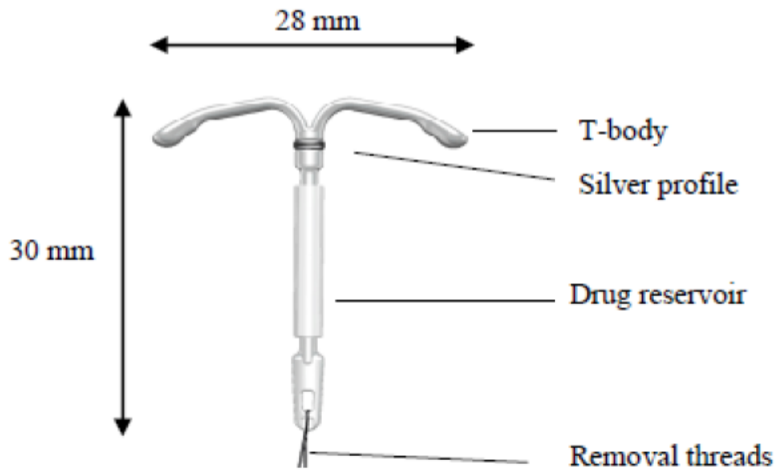

Figure 1. Schematic illustration of the intrauterine delivery system LCS12

The drug reservoir is composed of the drug core (b) (4) and the membrane (Figure 2). The drug core consists of a mixture of (b) (4) LNG and (b) (4) core base made of poly(dimethylsiloxane) (PDMS). The core is surrounded by a membrane (b) (4) LNG is present in (b) (4) the core (b) (4)

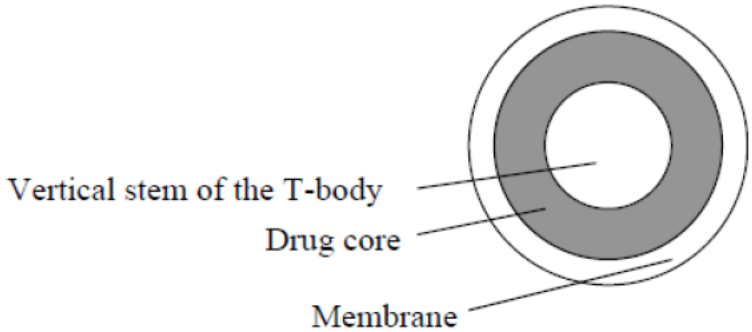

Figure 2. Schematic illustration of the cross section of LCS12

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Table 1 summarizes the composition of the final LCS formulation.

Table 1. Qualitative and Quantitative Composition of LCS 12 Commercial Formulation

Composition	Reference to standard	Function	Amount
Drug substance			
Levonorgestrel (b) (4)	Ph. Eur., USP	drug substance	13.5 mg
Excipients		(b) (4)	
Poly(dimethylsiloxane) elastomer core	specification		
Poly(dimethylsiloxane) elastomer silica filled	specification		
Other components			
T-Body [a]	specification	structural frame	(b) (4)
Thread [b]	specification	removal thread	
Silver profile (b) (4)	specification	facilitates detection by ultrasound	
Integrated administration device			
Inserter	specification	administration device	1 piece
(b) (4)			
Ethylene oxide	specification	sterilization gas	(b) (4)
(b) (4)	Ph. Eur., USP	(b) (4)	

[a] Polyethylene containing (b) (4) barium sulfate (Ph. Eur., USP)
[b] Polyethylene pigmented with (b) (4) iron oxide

Drug Product Development

During the phase 2 studies, two different formulations, LCS12 and LCS16, were investigated. In the phase 2 and phase 3 studies (A46796 and A52238, respectively) the same formulation of the (b) (4) of LCS12 and LCS16 was used, (b) (4)

For phase 3, the design of the T-body (b) (4) was adapted to (b) (4) These modifications led to revalidation and optimization of the assembly process (b) (4)

Further modifications of the T-body (b) (4) were implemented for phase 3b studies. The Applicant states that (b) (4) The overall development program for LCS12 and LCS16 and the data provided to support the bridging between formulations are summarized in Figure 3. Table 2 summarizes the differences between the compositions of the phase 2, phase 3a, and phase 3b/commercial formulations. Of note, although the LCS 16 was also tested in phase 3 clinical trials, this strength is not proposed to be marketed at this time.

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/s/

SANDRA SUAREZ
11/26/2012

ANGELICA DORANTES
11/26/2012