CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203159Orig1s000

PHARMACOLOGY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	203159
Supporting document/s:	SD#1, eCTD #0000; 12/9/2011 SD#6, eCTD #0005; 3/12/2012 IND 73505, SD#51, eCTD #0045; 8/31/2011 (original IND)
Applicant's letter date:	December 9, 2011
CDER stamp date:	December 9, 2011
Product:	LCS12 (levonorgestrel-releasing intrauterine system) 13.5 mg
Indication:	Prevention of pregnancy for up to 3 years
Applicant:	Bayer Health Care Pharmaceuticals Inc. P.O. Box 1000, Montville, NJ 07045-1000
Review Division:	Division of Reproductive and Urologic Products
Reviewer:	Kimberly Hatfield, PhD
Secondary Reviewer:	Alexander Jordan, PhD
Division Director:	Hylton Joffe, MD
Project Manager:	Charlene Williamson

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1 Executive Summary

1.1 Recommendations

1.1.1 Approvability

Nonclinical data support approval of LCS12, levonorgestrel intrauterine delivery system 13.5 mg, for the prevention of pregnancy for up to 3 years.

1.1.2 Additional Non Clinical Recommendations

No additional nonclinical studies are recommended.

1.1.3 Labeling

The Sponsor's proposed LCS12 (Skyla) labeling is modeled off of the approved physicians labeling for Mirena (Bayer is the Sponsor for both Mirena and Skyla). The Sponsor has proposed minor additions of language to Sections 8.1, 8.3 and 8.4, but these are based on clinical knowledge. All changes to Section 8 appear appropriate, and there are no objections.

The Sponsor has proposed no changes to the language in Section 13 (Carcinogenesis, Mutagenesis, Impairment of Fertility) from that of Mirena, other than the change in dose multiple values, which are all accurate. However, a change in wording is proposed by the review team to conform to the labeling in this Section of oral contraceptive products. This change would delete (b) (4) and only refer to the Warnings and Precautions Section 5.8 regarding Breast Cancer. This will also be proposed for Mirena.

The pharmacologic class is incorrect as currently listed in Highlights of Prescribing Information, and should be edited based on the FDA Established Pharmacologic Class listings. The word (b) (4) should not be used, and while the Established Pharmacologic Class listing suggests the use of the term IUD, the term IUS is more appropriate, as this is technically a drug product and not a device. Recommended labeling is shown below, while annotated labeling can be found beginning on page 41 of this review.

INDICATIONS AND USAGE
Skyla is a progestin-containing intrauterine system (IUS) indicated for prevention of pregnancy for up to 3 years (1)

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
The use of Skyla during an existing or suspected pregnancy is contraindicated. Many studies have found no harmful effects on fetal development associated with long-term use of contraceptive doses of oral progestins. The few studies of infant growth and development that have been conducted with progestin-only

pills have not demonstrated significant adverse effects. *[See Contraindications (4), Warnings and Precautions (5.1, 5.2).]*

8.3 Nursing Mothers
In general, no adverse effects have been found on breastfeeding performance or on the health, growth, or development of the infant. Isolated postmarketing cases of decreased milk production have been reported among women using progestin-only birth control pills. Small amounts of progestins pass into the breast milk of nursing mothers resulting in detectable steroid levels in infant serum. *[See Warnings and Precautions (5.5).]*

8.4 Pediatric Use
Safety and efficacy of Skyla have been established in women of reproductive age. Safety and efficacy is expected to be the same for postpubertal adolescents under the age of 18 as for users 18 years and older. Use of this product before menarche is not indicated.

13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
[See Warnings and Precautions (5.8).]

1.2 Brief Discussion of Nonclinical Findings

LCS12 (LNG-IUS) is a drug-delivery device designed for intrauterine insertion, releasing small amounts of levonorgestrel (LNG) over time, conferring its long term contraceptive effect. LCS12 is modeled after the approved intrauterine system (IUS) Mirena, but is designed to deliver a lower dose of LNG than Mirena, once inserted (10 μg/day versus 20 μg/day). Both the LCS device and the active drug have been evaluated in nonclinical studies for safety and tolerability. LNG has a well-documented safety profile based on over 30 years of clinical use; therefore, no studies were conducted by the Sponsor to evaluate the safety of LNG. A number of acute toxicity, mutagenicity, and tolerability studies were performed on the components of LCS12, along with a chronic 9-month toxicity study where a modified LCS12 was implanted in female monkeys, in order to evaluate the safety and tolerability of the product during insertion, and long-term implantation in the uterine cavity.

The 3 components of the inserter (insertion tube, flange and plunger) were well-tolerated following intracutaneous administration, and had no skin sensitization or cytotoxic potential. The silver component of the T-body (for detection via ultrasound) was well-tolerated with no signs of toxicity based on single i.v., i.p. and i.c. administration, and 13 weeks (intrauterine) administration; was not an irritant or skin-sensitizer, and was not mutagenic. Intrauterine administration of a modified LCS12 (for size purposes) in the monkey resulted in pharmacologic effects, but no local tolerance or safety issues. Therefore, the LCS12 product itself was deemed safe.

Extracts of the silver ring do however possess cytotoxic potential, but this is not expected to be a concern during clinical use. The estimated concentrations of silver in

the extracts that caused cytotoxic potential are approximately 13-20 times higher than the amount of silver found to be released in an in vitro release test. A non-cytotoxic extract of silver had a concentration approximately 6-fold higher than that determined from the *in vitro* release test. Since there is no other toxicity, intolerance or mutagenicity noted for the silver component, the use of silver in the LCS12 T-body for ultrasound detection is not a safety concern. Calculations determined that the daily release of silver from LCS12 is at least 3000 times lower than the EPA's established oral reference dose for silver (an estimate of a daily exposure to the human population that is likely to be without an appreciable risk of deleterious effects during a lifetime).

Toxicokinetic comparisons between clinical and nonclinical use were based on values determined in the 9-month intrauterine monkey study (using a modified LCS12 product (based on size) that released 16 μg/day), and Phase 2 and Phase 3 clinical PK data. Based on AUC, the 16 μg/d release rate dose in the monkey is 8-9 times higher than the planned LCS12 clinical dose, and was found to have no toxicity or safety issues. In addition, since the daily release rate of LNG from LCS12 is lower than that of Mirena, this also supports the clinical safety of the chosen dose.

2 Drug Information

2.1 Drug

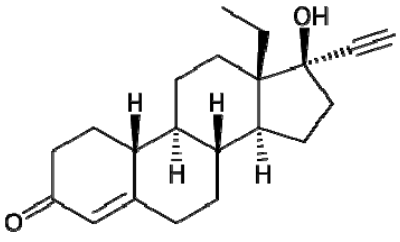
2.1.1 CAS Registry Number: 797-63-7

2.1.2 Generic Name: Levonorgestrel intrauterine delivery system 13.5 mg (LNG-IUS or LCS12)

2.1.4 Chemical Name: 18,19-Dinorpregn-4-en-20-yn-3-one, 13-ethyl-17-hydroxy-, (17a)-(-)

2.1.5 Molecular Formula/Molecular Weight: $C_{21}H_{28}O_2$; MW = 312.45 g/mol

2.1.6 Structure



2.1.7 Pharmacologic class: Progestin-releasing intrauterine system

2.2 Relevant IND/s, NDA/s, and DMF/s

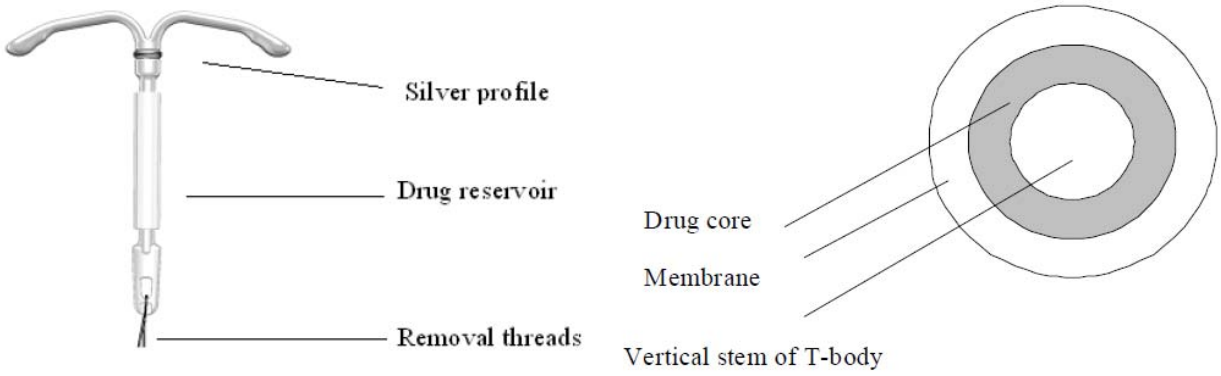
IND 73505: Levonorgestrel Intrauterine System (Bayer Health Care Pharmaceuticals Inc)
NDA 21225: Mirena® (Bayer Health Care Pharmaceuticals Inc)
DMF 4178: Levonorgestrel (Bayer Pharma AG)

2.3 Clinical Formulation

2.3.1 Drug Formulation

This product is an intrauterine delivery system (IUS) consisting of a whitish or pale yellow drug reservoir mounted on the vertical stem of a T-body (Figure 1). The drug reservoir consists of a core of (b) (4) levonorgestrel (LNG) and (b) (4) poly(dimethyl-siloxane) elastomer, covered with poly(dimethylsiloxane) membrane (b) (4) A silver ring is attached to the upper end of the vertical stem for ultrasound detection. The T-body has a loop at one end and two arms at the other end. Removal threads are attached to the loop. The inserter components are insertion tube, plunger, flange, handle, slider, and thread lock (Figure 2).

Figure 1: Schematic illustration of the system



T-Body Cross-section of the drug reservoir

Figure 2: Schematic illustration of the integrated inserter

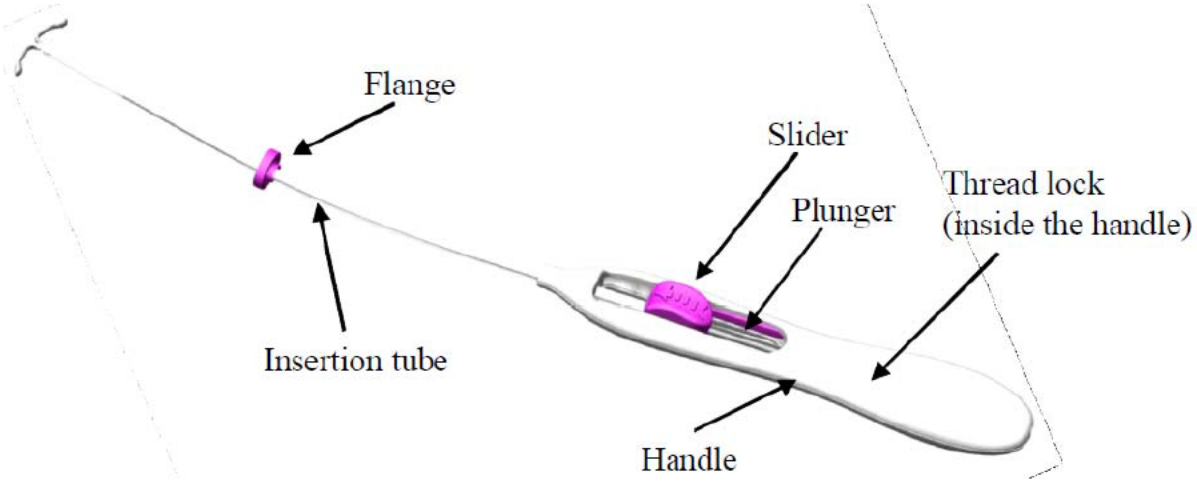


Table 1: Composition of the LNG-IUS (LCS12)

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			(b) (4)
T-Body [a]	specification	structural frame	
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)			(b) (4)
Ethylene oxide (b) (4)	specification Ph. Eur., USP	sterilization gas (b) (4)	

a Polyethylene (Ph. Eur. 3.1.3, Commission Regulation (EU) no. 10/2011) containing (b) (4) barium sulfate (Ph. Eur., USP)

b Polyethylene (Ph. Eur. 3.1.3, Commission Regulation (EU) no. 10/2011) pigmented with (b) (4) iron oxide (USP/NF, CFR21 Part 73.1200, Directive 2008/128/EC - E172)

Table 2: Qualitative composition of LNG-IUS 13.5 mg (LCS12)

Component/ description	Pre-clinical	Phase 2	Phase 3/phase 3b	Commercial product
Drug (b) (4) Composition (w/w) (b) (4)	(b) (4)			(b) (4)
Membrane (b) (4) Material				
Silver profile Composition				
T-Body Composition				
Removal thread Composition				

a Pre-clinical batches C97033 and C97034 consisted of (b) (4) Pre-clinical batch no. C99018 consisted of (b) (4)

b PDMS = poly(dimethylsiloxane)

2.3.2 Comments on Novel Excipients

A silver ring is included on the T-body for ease of detection of the IUS by ultrasound. The toxicity of this silver component has been evaluated in this review. The Sponsor notes that in vivo release of silver from the LCS is approximately 100 ng/day during a 3 year usage. In the Phase 3 study (A52238), after insertion of LCS12, the silver ion concentration in serum was always below the LLOQ of 1 µg/L.

2.3.3 Comments on Impurities/Degradants of Concern

None.

2.4 Proposed Clinical Population and Dosing Regimen

LCS12 is indicated to prevent pregnancy for up to 3 years. Compared to the Mirena treatment duration of 5 years, LCS12 is intended to provide contraceptive protection for women over a period of up to 3 years, with both a lower daily release rate of LNG, and a smaller size of the system (smaller insertion tube diameter and T-frame) than that of Mirena. The in vitro LNG release rate in weeks 3-4 is ~12 µg/24 hrs. The in vivo release rate is approximately 10 µg/24 hrs in weeks 3-4 and 5 µg/24 hrs after 3 years. The mean LNG in vivo release rate is approximately 6 µg/24 hrs over the period of 3 years. The treatment duration may be well suited for a young population, and the smaller size will facilitate successful insertion in nulliparous as well as parous women.

2.5 Regulatory Background

The LCS12 (LNG-IUS) product was developed based on considerable experience with Mirena (also owned by Bayer). The product was designed to be smaller in size than

Mirena and release a lower dose of LNG than Mirena (initial in vitro release rate 12 µg/d, initial in vivo release rate 10 µg/d). During Phase 2 clinical studies, two different doses of LNG were investigated, 12 and 16 µg/d (LCS12 and LCS16). The (b) (4) LNG content of LCS12 (b) (4) is (b) (4) 13.5 mg (b) (4)

Bayer authorizes cross reference to its own IND for this product (IND 73505), as well as its currently marketed product Mirena (NDA 21225). Appendix 1 (page 42) provides a tabular listing of study reports incorporated by reference to NDA 21225.

This NDA is being filed as a 505(b)(1) application. While the Sponsor is referencing studies conducted for the approval of Mirena (NDA 21225), the Sponsor (Bayer) owns this data and markets Mirena. Many of the same materials and components comprising LCS12 were studied nonclinically for Mirena, so these studies can be used to support this new product. All additional supportive studies have been submitted to the IND. As such, the nonclinical package is complete.

2.6 Codes

A number of the components/materials of the LNG IUS are identified by codes in the nonclinical studies. Table 3 lists the components with their corresponding code.

Table 3: Preclinical test codes of LNG-IUS (LCS12) and its components/materials

Preclinical code	Test article (component or material)
LE10900D [1]	(b) (4)
LE10200B [1]	
LE11600F [1]	
LE11601E [1]	
LE1002C [2]	
LE0027000C [1]	
LE1005C [2]	
LE10200J [2]	
LE1003C [2]	
LE11602A (placebo) [6] LE11601A (2 µg/day) [6] LE11600A (8 µg/day) [6]	

LE0420902N [7]	(b) (4)
LE11603A	
C08133	
PCU	
C08075_C	
C08075_A	

[1] same material used in Mirena
[2] material new in LCS12
[3] long-term body contact
[4] short-term body contact
[5] no body contact
[6] same composition as in the to-be-marketed product (T-body and reservoir)
[7] (b) (4) different (b) (4) but silver ring included

3 Studies Submitted

3.1 Studies Reviewed

Studies submitted in current NDA:

(All studies were submitted under IND 73505, SD#51, eCTD #0045; 8/31/2011)

A45907 - C08075_A (EtO steril) [Extract] Acute toxicity in mice (M/F) after single intravenous administration of an extract
A45906 - C08075_A (EtO steril) [Extract] Acute toxicity in mice (M/F) after single intra-peritoneal administration of an extract
A24173 - LE0420902N 9 months local and systemic tolerance study in female monkeys with an intrauterine levonorgestrel releasing system inserted into the uterus
A45408 - C08075_C Drug-free Mirena (b) (4) Local and systemic tolerance study in monkeys over a period of ca. 13 weeks after surgical intrauterine insertion of an intrauterine system
A45666 - Forward cell mutation assay with extracts of C08075_A ((b) (4) at the thymidine kinase locus (TK+/-) in mouse lymphoma L5178Y cells
A45701 - Evaluation of extracts of C08075_A ((b) (4) in a bacterial reverse mutation study using Salmonella typhimurium (Ames Test)
A44181 - LE10200J [Extract] Local tolerance test after single intracutaneous administration in the rabbit
A51744 - LE1005C (MIRENA (b) (4) Tube) [Extract] Local tolerance test after single intracutaneous administration in the rabbit
A52066 - LE1003C (LCS (b) (4) (b) (4) [Extract] Local tolerance test after single intracutaneous administration in the rabbit
A45905 - C08075_A (EtO steril) [Extract] Local tolerance test after single intracutaneous administration in the rabbit
A46336 - C08133 (EtO steril) Local tolerance test after intramuscular implantation in the rabbit with an exposure period of 8 days

PH-35585 - LE10200J Study for the skin sensitization effect in guinea pigs
PH-36388 - Mirena (b) (4) Insertion Tube Study for the skin sensitization effect in guinea pigs
PH-36404 - LE1003C Study for the skin sensitization effect in guinea pigs
PH-35865 - C08075_A (b) (4) Study for the skin sensitization effect in guinea pigs
A52604 - Cytotoxicity assay in vitro: Evaluation of materials for medical devices (XTT-Test) with LE1005C
A52537 - Cytotoxicity assay in vitro: Evaluation of materials for medical devices (XTT-Test) with LE1003C
A46671 - Cytotoxicity assay in vitro: Evaluation of materials for medical devices (XTT-Test) with C08075_A (b) (4) and C08075_A (b) (4)
A51186 - Cytotoxicity assay in vitro: Evaluation of materials for medical devices (XTT-Test) with LE1002C (extraction period: 28 days)
A51185 - Cytotoxicity assay in vitro: Evaluation of materials for medical devices (XTT-Test) with LE1002C (extraction period: 72 hours)
A46674 - Detection of the haemolytic potential of an extract of C08075_A_ (b) (4) with human erythrocytes
A45288 - LCS/Silver ion release in vitro

Studies submitted with initial IND (reviewed by Krishan Raheja, DVM, PhD):

A16460 ((b) (4) study #56151 Schering Oy #MP00270-23684-01) - LE0027000C (EtO steril.): In vitro cytotoxicity test (Elution test)
A16463 ((b) (4) study #56152 Schering Oy #MP00270-23685-01) - LE0027000C (EtO steril.): Hemolysis test (Direct contact test)
A16464 ((b) (4) study #56148) - LE0027000C (Ethylene oxide sterilized) Pyrogen test in rabbits
A16465 (TXEX20040021) - Salmonella Typhimurium Reverse Mutation Assay with Extracts of LE0027000C (EtO steril)
A16466 (TXEX20040022) - Cell mutation assay at the thymidine kinase locus (TK +/-) in mouse lymphoma L5178Y cells with extracts of LE0027000C (EtO steril)
A16467 (TXST20040138) - Maximization test in the guinea-pig to determine a sensitizing effect (delayed hypersensitivity) of LE0027000C (EtO steril)
A16468 (TXST20040139) - LE0027000C (EtO steril) [Extract] Local tolerance test after single intracutaneous administration in the rabbit
A16469 (TXST20040136) - LE0027000C (EtO steril) - Acute toxicity in mice (M/F) after single i.v. administration
A16470 (TXST20040137) - LE0027000C (EtO steril) Acute toxicity in mice (M/F) after single intra-peritoneal administration of an extract
A16471 (TXST20040140) - LE0027000C (EtO steril) - Local tolerance test after intramuscular implantation in the rabbit with an exposure period of 8 days
A16472 (TXST20040141) - LE0027000C (EtO steril) - Local tolerance test after intramuscular implantation in the rabbit with an exposure period of 90 days (at least)

A16473 (TXST20040105) - LE0027000C (EtO steril) - Systemic and local tolerance study in rats after subcutaneous implantation of the test article over 4 or 26 to 27 weeks

Studies also submitted to NDA 21225 (Mirena) and already reviewed:

A44272 - Cytotoxicity assay in vitro: Evaluation of materials for medical devices (XTT-Test) with LE10200J (b) (4) (reviewed by Kimberly Hatfield, 1-28-09, in association with NDA 21225, SDN#23 (eCTD #0016), 11-19-2008)

3.2 Studies Not Reviewed

A52522 - Concentrations of ZK 65223 (silver) in Study "Cytotoxicity assay in vitro: Evaluation of materials for medical devices (XTT-Test) with LE1002C (extraction period: 28 days)"
-this is a partial report in support of study A51186

3.3 Previous Reviews Referenced

Initial IND, IND 73505, SD#6, 7-27-2007:
Reviewed by Krishan Raheja, DVM, PhD; 10-1-2007
NDA 21225, SD#23, 11-19-2008:
Reviewed by Kimberly Hatfield, PhD; 1-28-2009

4 Pharmacology

4.1 Primary Pharmacology

LNG has been extensively used as an approved product in a variety of oral contraceptives, hormone replacement therapy and LNG-releasing intrauterine systems, and its pharmacology is well known. LNG is a metabolically stabilized 19-nortestosterone derivative, a potent progestin, has some androgenic activity but is devoid of glucocorticoid and estrogenic activity in vivo, and is a potent inhibitor of ovulation. Despite the extensive knowledge regarding LNG, the Sponsor has cited numerous literature articles and has provided a literature summary of the pharmacodynamic properties of LNG with the initial IND 73505 (SD #6; 7-30-2007).

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

The pharmacokinetics and ADME of LNG in animals are well known. Despite this knowledge, the Sponsor has provided a literature summary of the pharmacokinetic properties of LNG with the initial IND 73505 (SD #6; 7-30-2007), and in the nonclinical overview of this application.

5.2 Toxicokinetics

The toxicokinetics of the LNG IUS have been studied in monkeys. See Study Report A24173 "LE0420902N 9 months local and systemic tolerance study in female monkeys with an intrauterine levonorgestrel releasing system inserted into the uterus" in Section 6.2 Repeat Dose Toxicity (page 15).

6 General Toxicology

6.1 Single-Dose Toxicity

Study title: C08075_A (EtO steril) [Extract] Acute toxicity in mice (M/F) after single intravenous administration of an extract

Study no.:	TOXT1079997 (Report A45907)
Study report location:	IND 73505; SD#51 (eCTD #45); 8-31-2011
Conducting laboratory and location:	Bayer Schering Pharma AG, Nonclinical Drug Safety, 13342 Berlin, Germany
Date of study initiation:	March 4, 2009
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	C08075_A (EtO steril) (b) (4) ; Batch C08136 ((b) (4) C08069 (silver) Control: 0.9% NaCl-solution

This study examined the toxicity of a single i.v. administration (50mL/kg) of saline control or an extract of C08075_A (b) (4) in 0.9% NaCl-solution (no concentration given). Each treatment group had 3 male and 3 female Crl:CD1 mice. Clinical observations and body weights were examined over a 14 day period. No test-article related findings were observed. A single i.v. administration of a C08075_A extract is tolerated in male and female mice with no signs of toxicity.

Study title: C08075_A (EtO steril) [Extract] Acute toxicity in mice (M/F) after single intra-peritoneal administration of an extract

Study no.:	TOXT0079996 (Report A45906)
Study report location:	IND 73505; SD#51 (eCTD #45); 8-31-2011
Conducting laboratory and location:	Bayer Schering Pharma AG, Nonclinical Drug Safety, 13342 Berlin, Germany
Date of study initiation:	March 4, 2009
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	C08075_A (EtO steril) ((b) (4) Batch C08136 (b) (4) C08069 (silver) Control: sesame oil

This study examined the toxicity of a single i.p. administration (50mL/kg) of sesame oil control or an extract of C08075_A (b) (4) in sesame oil (no concentration given). Each treatment group had 3 male and 3 female Crl:CD1 mice. Clinical observations and body weights were examined over a 14 day period. No test-article related findings were observed. A single i.p. administration of a C08075_A extract is tolerated in male and female mice with no signs of toxicity.

6.2 Repeat-Dose Toxicity

Study title: LE0420902N – 9 months local and systemic tolerance study in female monkeys with an intrauterine levonorgestrel (LNG) releasing system inserted into the uterus.

Study no.:	TXST20050085 (Report A24173)
Study report location:	IND 73505; SD#51 (eCTD #45); 8-31-2011
Conducting laboratory and location:	Bayer Schering Pharma AG, Nonclinical Drug Safety, 13342 Berlin, Germany
Date of study initiation:	July 11, 2005
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	ZK 18206 (levonorgestrel; LNG); LE0420902N (LNG IUS); Batch #C05058

Key Study Findings

- This study was conducted to test the local and systemic tolerance of the LCS device with the addition of the silver ring.
- Intrauterine administration of LNG-IUS resulted in pharmacologically-relevant outcomes in the uterus compared to placebo and sham controls, and expected mechanical effects of the IUS itself.
- There were no local tolerance or safety issues with LNG-IUS over 9 months use.

Methods

Doses:	0 (sham); 0 (placebo); 16 μg/d IUS (release rate)
Frequency of dosing:	Single administration, but 9 month exposure
Route of administration:	Intrauterine
Dose volume:	n/a
Formulation/Vehicle:	LE0420900N (placebo IUS); LE0420902N (LCS IUS)
Species/Strain:	Female cynomolgus monkey
Number/Sex/Group:	3 groups; 8 females/group
Age:	44-6 months
Weight:	2.2-4.1 kg
Satellite groups:	n/a

Unique study design:	The IUS could not be inserted in the monkey as in a human, due to size and the anatomy of the monkey's cervix. Therefore, the IUS was shortened, and inserted surgically into the cavum uteri and fixed in the myometrium (to inhibit rejection). Insertion was performend within one week after the end of a menstrual bleeding.
Deviation from study protocol:	n/a

Observations and Results

Mortality: All animals survived until scheduled termination of the study.

Clinical Signs: Both sham and placebo animals had a high number of observations of stained/bloody vaginal discharge compared to animals with the LNG IUS (407 (8 animals) in sham; 726 (8 animals) in placebo; 43 (4 animals) in LNG IUS). There were no other test-article related effects.

Menstrual Cycle Pattern: The normal monkey menstrual cycle is 29-30 days. All animals had normal cycling over 6 weeks pre-study. In sham and placebo groups, 6/8 animals each had vaginal bleeding during week 1, and then cycled normally during the remainder of the study. In LNG-IUS animals, 2/8 had vaginal bleeding during week 1, with 1 having no other menses through study end; 4/8 had no menstrual bleeding throughout study; 1/8 had a menses week 3/4, then nothing through study end. As such, it appears that LNG-IUS significantly decreases menstrual bleeding.

Body Weights: LNG-IUS animals had a 31% increase in mean absolute body weight versus sham control and 25% over placebo controls at the end of the study (40 weeks). Body weight gain was increased in LNG-IUS animals 2-fold over both sham and placebo controls. LNG-IUS gained 35% weight over 40 weeks, while sham and placebo controls only gained 19%. During study, LNG-IUS animals had statistically significant increases in absolute body weights versus sham controls from weeks 5-24 (LNG-IUS was not compared to placebo control week to week). However, there were no statistically significant increases in body weight gain from week to week in LNG-IUS animals versus sham controls.

Feed Consumption: LNG-IUS animals had a 13% increased mean daily food consumption (118.1 g/day) compared to placebo control (104.7 g/day), and 17% increase over sham control (101.3 g/day).

Ophthalmoscopy: No test article-related findings were observed.

Blood Pressure: A slight increase in systolic pressure was observed in LNG-IUS animals at week 39 versus sham controls, but was within the historical control range. Similar increases were also observed pre-study and in individual animals of sham and placebo at different time points, so this does not appear be test article-related.

ECG and Heart Rate: No test article-related findings were observed.

Hematology: No test article-related findings were observed.

Clinical Chemistry: Compared to sham controls, LNG-IUS animals showed slight statistically significant increases in total protein at weeks 26 (+8%) and 39 (+6%), and slight statistically significant increases in total alpha globulin percentage at weeks 26 (-15%) and 39 (-16%). GGT was statistically significantly increased by 31% at week 39 (study end) in LNG-IUS animals, and throughout the study (21-31%, varying statistical significance), but pre-study values were also elevated in these animals (+28%) compared to sham controls.

Urinalysis: No test article-related findings were observed.

Coagulation: No test article-related findings were observed.

Gross Pathology: In the placebo control group, the IUS was undetectable in 3/8 animals. All LNG-IUS animals had a detectable IUS. For LNG-IUS animals, 3/8 had discolored uteri, 5/8 had uteri with thickened inner surface, and 3/8 had reddening in the uteri. The uterine findings are likely treatment-related and pharmacological.

Organ Weights: No test article-related findings were observed.

Histopathology: Adequate Battery: Yes Peer Review: Yes
Histological Findings: Uterine findings were generally pharmacological in LNG-IUS animals. However, in the uteri of LNG-IUS animals, 1/8 had moderate decidual area necrosis, 2/8 had slight hemorrhage, and 2/8 had slight erosion/necrosis. Other findings of note in LNG-IUS animals were: 1) 4/8 with slight diffuse fatty change in the liver; 2) 2/8 with moderate/marked focal fatty change in the liver. The Sponsor attributes these liver findings to increased food consumption, and increased body weights in these animals.

Toxicokinetics: The following TK parameters were observed in LNG-IUS animals:

	Cmax (ng/mL)	Tmax (h)	$AUC_{(0\text{-}tlast)}$ (ng/mL*h)	T_{last} (h)	C_{av} (ng/mL)	C_{ss} (ng/mL)
LNG-IUS	19.1 ± 6.96	***24 ± 24***	16893 ± 5692	***6696 ± 6576***	2.52 ± 0.828	2.30 ± 0.764

Values represent the mean ± SD, except for T_{max} and T_{last} (bold, italic) that represent median, and minimum for SD.
T_{last} = last sampling time with concentration value >LLOQ
C_{av}= average serum concentration
C_{ss} = serum concentration at steady state (week 5-40/41)

In addition, it was noted that the mean concentration of LNG in uterine tissue was 29.8 ± 15 pg/mg.

One error of the TK study was that LNG was detectable in the first serum sample of 7/8 placebo animals (24 h after implantation), but no detectable levels in the uterine tissue. The Sponsor cannot explain these findings, as contamination of the IUS, before, or during surgery were unlikely based on study protocols. However, LNG was not detected at any other time point, and these results did not likely affect the validity of the study.

Study title: C08075_C, Drug-free Mirena (b) (4) Local and systemic tolerance study in monkeys over a period of ca. 13 weeks after surgical intrauterine insertion of an intrauterine system.

Study no.:	TOXT9079931 (Report #A45408)
Study report location:	IND 73505; SD#51 (eCTD #45); 8-31-2011
Conducting laboratory and location:	Bayer Schering Pharma AG, Nonclinical Drug Safety, 13342 Berlin, Germany
Date of study initiation:	January 16, 2009
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	C08075_C; Batch C08135 (b) (4) C08069 (silver) LE0060701R (negative std ref material); Batch H-071

Objective: This study assessed the safety of C08075_C, (b) (4) There is no LNG present.

Methods: Two groups of 4 female cynomolgus monkeys were tested: one group with C08075_C implanted into the uterus, and the second group with LE0060701R (reference material) implanted into the uterus (control). Standard repeat dose study parameters were assessed to examine the effects of intrauterine implantation, and necropsy was performed at 13 weeks.

Results: No test-article-related effects on clinical observations, food consumption, body weight, body weight gain, body temperature, blood pressure, ECG, hematology, clinical chemistry, urinalysis, coagulation, organ weights or histopathology. Some intrauterine histopathology was evident, but was related to the IUS being fixed by suture to the uterus (pressure or mechanical irritation). The IUS device was present in the uterine lumen of each animal.

Conclusion: The C08075_C material is well-tolerated in the monkey over 13 weeks, with no compound-related effects.

7 Genetic Toxicology

7.1 *In Vitro* Reverse Mutation Assay in Bacterial Cells (Ames)

Study title: Evaluation of extracts of C08075_A (b) (4) in a bacterial reverse mutation study using Salmonella typhimurium (Ames Test)

Study no.:	TOXT7079975 (Report #A45701)
Study report location:	IND 73505; SD#51 (eCTD #45); 8-31-2011
Conducting laboratory and location:	Bayer Schering Pharma AG, Nonclinical Drug Safety, 13342 Berlin, Germany
Date of study initiation:	February 12, 2009
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	C08075_A (b) (4) Batch C08136 (b) (4) C08069 (silver)

Methods

Strains:	TA98, TA100, TA1535, TA1537, TA102
Concentrations in definitive study:	10-100%
Basis of concentration selection:	unknown
Metabolic activation system:	S9 fraction isolated from livers of Aroclor 1254 induced male Sprague Dawley rats
Negative control:	Direct plate incorporation: 70% EtOH or DMSO Preincubation modification: 0.9% NaCl or PB (phosphate buffer)
Positive control:	-S9: 2NF (2-nitro-9H-fluorene; 10µg); NaN_3 (sodium azide; 5µg); 4NPDA (4-nitro-o-phenylenediamine; 10µg); MMC (mitomycin C; 0.2µg), Cum (cumene hydroperoxide; 50µg) +S9: 2AA (anthracene-1-amine; 2.5µg or 10µg); BP (benzo[a]pyrene; 2.5µg); CP (cyclophosphamide; 400µg), DMNA (N-nitrosodimethylamine; 5µL)
Formulation/Vehicle:	Extract in 70% EtOH (incubation at 50°C for 72h) for direct plate incorporation procedure. Extract in 0.9% (w/v) NaCl-solution (incubation at 50°C for 72h) for preincubation modification.
Incubation & sampling time:	Direct plate incorporation: 37°C for 48 h (TA102) or 72 h (TA98, TA100, TA1535, TA1537) with or without S9. Preincubation: 37°C for 60 min, followed by incubation times as above.

Study Validity: Selection of bacterial tester strains was adequate. Positive controls produced expected responses. Dose selection for the plate incorporation method was adequate and included 10-100% test item extract per plate. The S9 concentration was within acceptable limits.

Results: The test item did not cause increased reversion in any of the tester strains at any dose, either by the plate incorporation procedure or through preincubation, in the absence or presence of S9. Positive and negative controls caused expected reversion.

Conclusion: The C08075_A material to be used in the IUS is not a mutagen based on the Ames test. It does not induce gene mutations by base-pair changes or frame-shifts in the genome of S. typhimurium strains.

Study title: Forward cell mutation assay with extracts of C08075_A at the thymidine locus ($TK^{+/-}$) in mouse lymphoma L5178Y cells

Study no.:	TOXT5079973 (Report #A45666)
Study report location:	IND 73505; SD#51 (eCTD #45); 8-31-2011
Conducting laboratory and location:	Bayer Schering Pharma AG, Nonclinical Drug Safety, 13342 Berlin, Germany
Date of study initiation:	February 10, 2009
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	C08075_A (b) (4) Batch C08136 (b) (4) C08069 (silver)

Methods

Cell line:	Mouse lymphoma L5178Y/$TK^{+/-}$
Concentrations in definitive study:	12.5-100% (-S9); 12.5-95% (+S9)
Basis of concentration selection:	Experience from prior studies with extracts in culture medium
Metabolic activation system:	S9 fraction isolated from livers of Aroclor 1254 induced male Sprague Dawley rats
Negative control:	Medium 1% DMSO (dimethysulfoxide)
Positive control:	NQO (4-nitroquinoline 1-oxide; 0.1 μg/mL) and 3-MC (3-methylcholanthrene; 2 μg/mL)
Formulation/Vehicle:	Assay 1: Extracts in culture medium RPMI 1640 with Gluta-MAX-I + 5% horse serum + 100 U/100 μg/mL penicillin streptomycin Assay 2: Extracts in culture medium RPMI 1640 with Gluta-MAX-I + 20% horse serum + 100 U/100 μg/mL penicillin streptomycin

Incubation & sampling time: 3hrs at 37°C with and without S9; 24hrs at 37°C without S9. Following treatment, test item was removed, and cells subcultured fro a 2-d growth and expression period. Cells were then plated in microtiter plates and incubated at least 10 days at 37°C and 5% CO_2.

Study Validity: The study was valid as all criteria were met: 1) at least one negative and/or solvent control and one positive control is completely valuable, 2) the negative and/or solvent controls yield values in the 1st and 2nd plating efficiency in a range of 65-130%; 3) the means of the spontaneous mutant frequency of the negative and/or solvent controls are in ta range of 5-170 per 106 cells and in accordance with historical control data; and 4) positive controls induce significant increases (at least 2-fold) in the mutant frequencies compared to the negative controls and yield absolute values above the range of historical control data.

Results: There were no cytotoxic effects of the test item in assays with or without S9. In assays #1 and #2, there were no concentrations of test article that resulted in an increase in mutant frequencies that exceeded the threshold of twice the number of mutant colonies of the solvent controls. The NQO and 3-MC positive controls were clearly mutagenic.

Conclusion: The C08075_A material to be used in the IUS is not a mutagen based on the mouse lymphoma assay.

Table 4: Summary of Assay #1: Pulse treatment (3h) with and without S9 mix (mean values of two independent cultures) with extracts of C08075_A in culture medium (5% horse serum)

		Concentr. per mL	S9 mix	1. PE relative (%)	SG relative (%)	Relative total growth (%)	2. PE absolute (%)	Mutants per 10^6 cells	Mutation index
Negative control	Medium		-	100	100	100	74	91	1.0
Solvent control	DMSO	1 %	-	100	100	100	86	94	1.0
	Test item a)	12.5 %	-	88	100	109	80	67	0.7
		25 %	-	103	97	95	72	88	1.0
		50 %	-	93	95	87	68	76	0.8
		100 %	-	95	93	88	70	85	0.9
Positive control	NQO	0.1 µg	-	53	86	52	52	767	8.2
Negative control	Medium		+	100	100	100	101	140	1.0
Solvent control	DMSO	1 %	+	100	100	100	98	131	1.0
	Test item a)	12.5 %	+	91	104	108	105	108	0.8
		25 %	+	91	102	95	94	105	0.8
		50 %	+	87	102	88	87	121	0.9
		95 %	+	87	100	92	93	115	0.8
Positive control	3-MC	2 µg	+	71	97	84	85	636	4.9

S9 = liver homogenate (9000xg fraction) derived from male rats; PE = plating efficiency; SG = suspension growth; a) = extract of C08075_A in culture medium (5% horse serum) for 72 h at 37°C.

Table 5: Summary of Assay #2: Continuous treatment (24h) without S9 mix; Pulse treatment (3h) with S9 mix (mean values of two independent cultures) with extracts of C08075_A in culture medium (20% horse serum)

		Concentr. per mL	S9 mix	1. PE relative (%)	SG relative (%)	Relative total growth (%)	2. PE absolute (%)	Mutants per 10^8 cells	Mutation index
Negative control	Medium		-	100	100	100	102	72	1.0
Solvent control	DMSO	1 %	-	100	100	100	102	76	1.0
	Test item [a)]	12.5 %	-	99	104	107	104	70	1.0
		25 %	-	93	104	114	111	55	0.8
		50 %	-	104	102	102	102	77	1.1
		100 %	-	98	93	94	104	78	1.1
Positive control	NQO	0.025 µg	-	73	111	102	94	418	5.5
Negative control	Medium		+	100	100	100	109	77	1.0
Solvent control	DMSO	1 %	+	100	100	100	112	65	1.0
	Test item [a)]	12.5 %	+	97	103	96	102	69	0.9
		25 %	+	98	104	83	87	84	1.1
		50 %	+	103	106	97	100	72	0.9
		95 %	+	99	101	93	100	61	0.8
Positive control	3-MC	2 µg	+	72	86	60	78	535	8.2

S9 = liver homogenate (9000xg fraction) derived from male rats; PE = plating efficiency; SG = suspension growth; a) = extract of C08075_A in culture medium (20% horse serum) for 72 h at 37°C.

10 Special Toxicology Studies

Study title: LE10200J [Extract] Local tolerance test after single intracutaneous administration in the rabbit

Study no.:	TOXT3079106 (Report #A44181)
Study report location:	IND 73505; SD #51 (eCTD #45); 8-31-2011
Conducting laboratory and location:	Bayer Schering Pharma AG, Nonclinical Drug Safety, 13342 Berlin, Germany
Date of study initiation:	September 17, 2008
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	LE10200J (Batch #C08039) (EtO steril) in aqueous (0.9% NaCl) and oily (sesame oil) extracts. (b) (4)

This study examined the local tolerance of single intracutaneous administration of saline or sesame oil extracts of LE10200J (and controls). Two male and two female New Zealand white rabbits were tested, with each animal receiving 5 injections with 0.2mL of

the LE10200J extract in sesame oil on the right side of the spine, and 5 injections with 0.2mL of extraction medium as control. On the left side of the spine, the same animals received the same number and amount of injections with LE10200J extract in 0.9% NaCl, and extraction medium. Reactions were observed immediately and at 4, 24, 48, and 72 hrs post-injection, and once daily until day 29 (until no findings observed). The test article had no effect on body weight. No test-article related findings were observed either with saline extract or sesame oil extract. Slight reddening or irritations were also observed with control treatment. Therefore, LE10200J extracts are tolerated following intracutaneous administration.

Study title: LE1005C (Mirena (b) (4) Tube) [Extract] Local tolerance test after single intracutaneous administration in the rabbit

Study no.:	TOXT7082124 (Report #A51744)
Study report location:	IND 73505; SD #51 (eCTD #45); 8-31-2011
Conducting laboratory and location:	Bayer Schering Pharma AG, Nonclinical Drug Safety, 13342 Berlin, Germany
Date of study initiation:	October 16, 2010
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	LE1005C (Batch #TU006GT) (EtO steril) in aqueous (0.9% NaCl) and oily (sesame oil) extracts. (b) (4)

This study examined the local tolerance of single intracutaneous administration of saline or sesame oil extracts of LE1005C (and controls). Two male and two female New Zealand white rabbits were tested, with each animal receiving 5 injections with 0.2mL of the LE1005C extract in sesame oil on the right side of the spine, and 5 injections with 0.2mL of extraction medium as control. On the left side of the spine, the same animals received the same number and amount of injections with LE1005C extract in 0.9% NaCl, and extraction medium. Reactions were observed immediately and at 4, 24, 48, and 72 hrs post-injection, and once daily until day 18 (until no findings observed). The test article had no effect on body weight. No test-article related findings were observed either with saline extract or sesame oil extract. Slight reddening or irritations were also observed with control treatment. Therefore, LE1005C extracts are tolerated following intracutaneous administration.

Study title: LE1003C (LCS (b) (4) (b) (4) [Extract] Local tolerance test after single intracutaneous administration in the rabbit

Study no.:	TOXT8082125 (Report #A52066)
Study report location:	IND 73505; SD #51 (eCTD #45); 8-31-2011
Conducting laboratory and location:	Bayer Schering Pharma AG, Nonclinical Drug Safety, 13342 Berlin, Germany
Date of study initiation:	November 24, 2010
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	LE1003C (Batch #C10086) (EtO steril) in aqueous (0.9% NaCl) and oily (sesame oil) extracts. (b) (4)

This study examined the local tolerance of single intracutaneous administration of saline or sesame oil extracts of LE1003C (and controls). Two male and two female New Zealand white rabbits were tested, with each animal receiving 5 injections with 0.2mL of the LE1003C extract in sesame oil on the right side of the spine, and 5 injections with 0.2mL of extraction medium as control. On the left side of the spine, the same animals received the same number and amount of injections with LE1003C extract in 0.9% NaCl, and extraction medium. Reactions were observed immediately and at 4, 24, 48, and 72 hrs post-injection, and once daily until day 9 (until no findings observed). The test article had no effect on body weight. No test-article related findings were observed either with saline extract or sesame oil extract. Reddening or swelling were also observed with control treatment. Therefore, LE1003C extracts are tolerated following intracutaneous administration.

Study title: C08075_A (EtO steril) [Extract] Local tolerance test after single intracutaneous administration in the rabbit

Study no.:	TOXT9079995 (Report #A45905)
Study report location:	IND 73505; SD #51 (eCTD #45); 8-31-2011
Conducting laboratory and location:	Bayer Schering Pharma AG, Nonclinical Drug Safety, 13342 Berlin, Germany
Date of study initiation:	March 3, 2009
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	C08075_A (Batch #C08136) (EtO steril) in aqueous (0.9% NaCl) and oily (sesame oil) extracts. (b) (4)

This study examined the local tolerance of single intracutaneous administration of saline or sesame oil extracts of C08075_A (and controls). Two male and two female New Zealand white rabbits were tested, with each animal receiving 5 injections with 0.2mL of

the C08075_A extract in sesame oil on the right side of the spine, and 5 injections with 0.2mL of extraction medium as control. On the left side of the spine, the same animals received the same number and amount of injections with C08075_A extract in 0.9% NaCl, and extraction medium. Reactions were observed immediately and at 4, 24, 48, and 72 hrs post-injection, and once daily until no findings occurred. The test article had no effect on body weight. No marked test-article related findings were observed either with saline extract or sesame oil extract. Reddening, swelling or pain sensitivity were also observed with control treatment. Therefore, C08075_A extracts are tolerated following intracutaneous administration.

Study title: C08133 (EtO steril) Local tolerance test after intramuscular implantation in the rabbit with an exposure period of 8 days

Study no.:	TOXT7079966 (Report #A46336)
Study report location:	IND 73505; SD #51 (eCTD #45); 8-31-2011
Conducting laboratory and location:	Bayer Schering Pharma AG, Nonclinical Drug Safety, 13342 Berlin, Germany
Date of study initiation:	April 6, 2009
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	C08133 (Batch #C08133) (EtO steril) (b) (4) (C08133 (b) (4) Control: LE0060701R (Batch #H-071) (b) (4)

This study examined the local tolerance of intramuscular implantation of 4 test articles. Two male and two female New Zealand white rabbits were tested, with each animal having 4 test articles implanted into the sacrospinal muscle on the right side of the spine, and 4 control articles implanted on the left side. Local and systemic effects were evaluated by clinical parameters, necropsy, macroscopic and histopathological examination of the administration sites. The test article had no effect on body weight. One male had some swelling around the area of the skin cut, therefore it was determined not to be test-article-related, but due to mechanical trauma. Both control and test-article sites had slight fibrotic tissue and muscular necrosis with fibrosis (the latter mainly in the females). As these findings were equally present in controls, they were not test-article related. Therefore, C08133 was not an irritant.

Study title: LE10200J Study for the skin sensitization effect in guinea pigs (Guinea Pig Maximization Test)

Study no.:	T2079105 (Report #PH-35585)
Study report location:	IND 73505; SD #51 (eCTD #45); 8-31-2011
Conducting laboratory and location:	Bayer Healthcare AG, BSP-GDD-GED-GT-Special Toxicology, 42096 Wuppertal, Germany
Date of study initiation:	August 12, 2008
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	LE10200J (Batch #C08039) in aqueous (0.9% NaCl) or sesame oil extract (b) (4)

This study examined the skin-sensitizing effects of LE10200J in the guinea pig maximization test. Thirty female SPF-bred guinea pigs were treated with either control (0.9% (w/v) NaCl-solution (Group 1) or sesame oil (Group 2)) or test-article (LE10200J extract in 0.9% (w/v) NaCl-solution (Group 3) or sesame oil (Group 4)) at 100% concentration.

Methods: Intradermal induction – 6 intradermal injections (0.1mL each), 3 on each side of the neck region, were made according to the following:

Test Groups 3&4	Control Groups 1&2 and Dose-Finding Groups 5&6
a) complete Freund's adjuvant diluted in saline (1:1)	a) complete Freund's adjuvant diluted in saline
b) 100% LE 10200J	b) undiluted vehicle (saline or sesame oil)
c) 100% LE10200J & complete Freund's adjuvant (1:1)	c) 1:1 mixture Freund's adjuvant/vehicle

Topical induction – to provoke the possible sensitizing effect of LE10200J, on day 8, hypoallergenic patches treated with test item (0.5mL 100% LE10200J) or control (0.5mL vehicle) were placed between and on the injection sites for 48 hrs.
Topical challenge – on Day 22 (2 weeks after epidermal admin), a hypoallergenic patch loaded with 0.5mL 100% test-item or vehicle in saline or sesame oil was placed on the right flank of the animals of respective groups for 24 hrs. Reactions were assessed and graded 48 and 72hrs after the start of the application to induce the challenge. A substance was considered sensitizing if 30% or more of the test group animals reacted positively compared to controls.

Results: The appearance and behavior of the test-item group were not different from controls, and body weights were not different. Red wheels were observed in control and treated animals after the intradermal induction (after 48hrs), and encrustations were observed at the injection site of both control and treated animals after 7 days, then also from days 11-16. There were no skin effects of sensitization recorded for either control or treated animals.

Conclusion: LE10200J exhibits no skin-sensitization potential.

Study title: Mirena (b) (4) Insertion Tube: Study for the skin sensitization effect in guinea pigs (Guinea Pig Maximization Test)

Study no.:	T3081879 (Report #PH-36388)
Study report location:	IND 73505; SD #51 (eCTD #45); 8-31-2011
Conducting laboratory and location:	Bayer Schering Pharma AG, GDD-GED-GT-Special Toxicology, 42096 Wuppertal, Germany
Date of study initiation:	November 2, 2010
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	LE1005C (Batch #TU006Gt) in aqueous (0.9% NaCl) or sesame oil extract (b) (4)

This study examined the skin-sensitizing effects of LE1005C in the guinea pig maximization test. Thirty-four female SPF-bred guinea pigs were treated with either control (0.9% (w/v) NaCl-solution (Group 1) or sesame oil (Group 2)) or test-article (LE1005C extract in 0.9% (w/v) NaCl-solution (Group 3) or sesame oil (Group 4)) at 100% concentration.

Methods: Intradermal induction – 6 intradermal injections (0.1mL each), 3 on each side of the neck region, were made according to the following:

Test Groups 3&4	Control Groups 1&2 and Dose-Finding Groups 5&6
a) complete Freund's adjuvant diluted in saline (1:1)	a) complete Freund's adjuvant diluted in saline (1:1)
b) 100% LE1005C	b) undiluted vehicle (saline or sesame oil)
c) 100% LE1005C & complete Freund's adjuvant (1:1)	c) 1:1 mixture Freund's adjuvant/vehicle

Topical induction – to provoke the possible sensitizing effect of LE1005C, on day 8, hypoallergenic patches treated with test item (0.5mL 100% LE1005C) or control (0.5mL vehicle) were placed between and on the injection sites for 48 hrs.
Topical challenge – on Day 22 (2 weeks after epidermal admin), a hypoallergenic patch loaded with 0.5mL 100% test-item or vehicle in saline or sesame oil was placed on the right flank of the animals of respective groups for 24 hrs. Reactions were assessed and graded 48 and 72hrs after the start of the application to induce the challenge. A substance was considered sensitizing if 30% or more of the test group animals reacted positively compared to controls.

Results: The appearance and behavior of the test-item group were not different from controls, and body weights were not different. In control and test-item groups with saline, white wheals with red surrounding were observed, and in control and test-item groups with sesame oil, red wheals and white wheals with red surrounding were observed. Encrustations were observed at the injection site of both control and treated animals after 7 days. Upon topical challenge, no skin effect was observed in control or test-item groups.

Conclusion: LE1005C exhibits no skin-sensitization potential.

Study title: LE1003C: Study for the skin sensitization effect in guinea pigs (Guinea Pig Maximization Test)

Study no.:	T3081860 (Report #PH-36404)
Study report location:	IND 73505; SD #51 (eCTD #45); 8-31-2011
Conducting laboratory and location:	Bayer Schering Pharma AG, GDD-GED-GT-Special Toxicology, 42096 Wuppertal, Germany
Date of study initiation:	November 16, 2010
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	LE1003C (Batch #C10086) in aqueous (0.9% NaCl) or sesame oil extract (b) (4)

This study examined the skin-sensitizing effects of LE1003C in the guinea pig maximization test. Thirty-four female SPF-bred guinea pigs were treated with either control (0.9% (w/v) NaCl-solution (Group 1) or sesame oil (Group 2)) or test-article (LE1003C extract in 0.9% (w/v) NaCl-solution (Group 3) or sesame oil (Group 4)) at 100% concentration.

Methods: Intradermal induction – 6 intradermal injections (0.1mL each), 3 on each side of the neck region, were made according to the following:

Test Groups 3&4	Control Groups 1&2 and Dose-Finding Groups 5&6
a) complete Freund's adjuvant diluted in saline (1:1)	a) complete Freund's adjuvant diluted in saline (1:1)
b) 100% LE1003C	b) undiluted vehicle (saline or sesame oil)
c) 100% LE1003C & complete Freund's adjuvant 1:1	c) 1:1 mixture Freund's adjuvant/vehicle

Topical induction – to provoke the possible sensitizing effect of LE1003C, on day 8, hypoallergenic patches treated with test item (0.5mL 100% LE1003C) or control (0.5mL vehicle) were placed between and on the injection sites for 48 hrs.
Topical challenge – on Day 22 (2 weeks after epidermal admin), a hypoallergenic patch loaded with 0.5mL 100% test-item or vehicle in saline or sesame oil was placed on the right flank of the animals of respective groups for 24 hrs. Reactions were assessed and graded 48 and 72hrs after the start of the application to induce the challenge. A substance was considered sensitizing if 30% or more of the test group animals reacted positively compared to controls.

Results: The appearance and behavior of the test-item group were not different from controls, and body weights were not different. In control and test-item groups with saline, white wheals with red surrounding were observed, and in control and test-item groups with sesame oil, red wheals and white wheals with red surrounding were observed. Encrustations were observed at the injection site of both control and treated animals after 7 days, with wheals appearing in addition to encrustation in both test-item groups. Upon topical challenge, no skin effect was observed in control or test-item groups.

Conclusion: LE1003C exhibits no skin-sensitization potential.

Study title: C08075_A, (b) (4): Study for the skin sensitization effect in guinea pigs (Guinea Pig Maximization Test)

Study no.:	T2079402 (Report #PH-35865)
Study report location:	IND 73505; SD #51 (eCTD #45); 8-31-2011
Conducting laboratory and location:	Bayer Schering Pharma AG, GDD-GED-GT-Special Toxicology, 42096 Wuppertal, Germany
Date of study initiation:	February 17, 2009
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	C08075_A (Batch #C08136) in aqueous (0.9% NaCl) or sesame oil extract (b) (4)

This study examined the skin-sensitizing effects of C08075_A in the guinea pig maximization test. Thirty-four female SPF-bred guinea pigs were treated with either control (0.9% (w/v) NaCl-solution (Group 1) or sesame oil (Group 2)) or test-article (C08075_A extract in 0.9% (w/v) NaCl-solution (Group 3) or sesame oil (Group 4)) at 100% concentration.

Methods: Intradermal induction – 6 intradermal injections (0.1mL each), 3 on each side of the neck region, were made according to the following:

Test Groups 3&4	Control Groups 1&2 and Dose-Finding Groups 5&6
a) complete Freund's adjuvant diluted in saline (1:1)	a) complete Freund's adjuvant diluted in saline (1:1)
b) 100% C08075_A	b) undiluted vehicle (saline or sesame oil)
c) 100% C08075_A & complete Freund's adjuvant	c) 1:1 mixture Freund's adjuvant/vehicle

Topical induction – to provoke the possible sensitizing effect of C08075_A, on day 8, hypoallergenic patches treated with test item (0.5mL 100% C08075_A) or control (0.5mL vehicle) were placed between and on the injection sites for 48 hrs.
Topical challenge – on Day 22 (2 weeks after epidermal admin), a hypoallergenic patch loaded with 0.5mL 100% test-item or vehicle in saline or sesame oil was placed on the right flank of the animals of respective groups for 24 hrs. Reactions were assessed and graded 48 and 72hrs after the start of the application to induce the challenge. A substance was considered sensitizing if 30% or more of the test group animals reacted positively compared to controls.

Results: The appearance and behavior of the test-item group were not different from controls, and body weights were not different. In control and test-item groups red wheals were observed at 48 hours. After 7 days, in control and test-item groups with saline, encrustations were observed, and in control and test-item groups with sesame oil, wheals and encrustations were observed. Upon topical challenge, no skin effect was observed in control or test-item groups.

Conclusion: C08075_A exhibits no skin-sensitization potential.

Study title: Cytotoxicity assay in vitro: Evaluation of materials for medical devices (XTT-test) with LE1005C

Study no.:	T3081653EXT (Report #A52604)
Study report location:	IND 73505; SD #51 (eCTD #45); 8-31-2011
Conducting laboratory and location:	(b) (4)
Date of study initiation:	November 24, 2010
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	LE1005C(Batch #TU006GT) extracted in RPMI 1640 medium, supplemented with 10% FCS (PAA), 1mM sodium pyruvate, 2mM L-glutamine, and 100μg/mL penicillin/streptomycin. (b) (4)

This in vitro study was performed to assess the cytotoxic potential of LE1005C using the XTT test with an extract of the test item.

Cell line:	Mouse L929
Negative Control:	RM-C (high density polyethylene) (Lot# C-042) (100% of extract)
Positive Control:	Latex (Lot# 12200840820074) (3-100% of extract)
Medium Control:	Complete medium
Test item:	LE1005C (3-100% of extract)
Incubation time:	24 hours
Cytotox test:	50 μL XTT mixture added, then absorbance reading at 450 nm

There was no observed difference in absorbance reading between the negative control and medium control, and the positive control showed a distinct dose-related reduction in cell viability and proliferation (XTT_{50} = 18.3%). Absorbance readings for LE1005C did not indicate any cytotoxic effect up to the highest concentration of extract.

Conclusion: LE1005C does not possess cytotoxic potential.

Study title: Cytotoxicity assay in vitro: Evaluation of materials for medical devices (XTT-test) with LE1003C

Study no.:	T4081654EXT (Report #A52537)
Study report location:	IND 73505; SD #51 (eCTD #45); 8-31-2011
Conducting laboratory and location:	(b) (4)
Date of study initiation:	November 24, 2010
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	LE1003C(Batch #C10086) extracted in RPMI 1640 medium, supplemented with 10% FCS (PAA), 1mM sodium pyruvate, 2mM L-glutamine, and 100µg/mL penicillin/streptomycin. (b) (4)

This in vitro study was performed to assess the cytotoxic potential of LE1003C using the XTT test with an extract of the test item.

Cell line:	Mouse L929
Negative Control:	RM-C (high density polyethylene) (Lot# C-042) (100% of extract)
Positive Control:	Latex (Lot# 03200674110385) (3-100% of extract)
Medium Control:	Complete medium
Test item:	LE1003C (3-100% of extract)
Incubation time:	24 hours
Cytotox test:	50 µL XTT mixture added, then absorbance reading at 450 nm

There was no observed difference in absorbance reading between the negative control and medium control, and the positive control showed a distinct dose-related reduction in cell viability and proliferation (XTT_{50} = 6.6%). Absorbance readings for LE1003C did not indicate any cytotoxic effect up to the highest concentration of extract, and an XTT_{50} could not be calculated.

Conclusion: LE1003C does not possess cytotoxic potential.

Study title: Cytotoxicity assay in vitro: Evaluation of materials for medical devices (XTT-test) with C08075_A, (b) (4) and C08075_A, (b) (4)

Study no.:	T4078900EXT (Report #A46671)
Study report location:	IND 73505; SD #51 (eCTD #45); 8-31-2011
Conducting laboratory and location:	(b) (4)
Date of study initiation:	March 11, 2009
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	C08075_A, (b) (4) (Batch #C08136 (b) (4) and C08069(Ag)) extracted in RPMI 1640 medium, supplemented with 10% FCS, 1mM sodium pyruvate, 4mM L-glutamine, and 100µg/mL penicillin/streptomycin. (b) (4)

This in vitro study was performed to assess the cytotoxic potential of C08075_A, (b) (4) and C08075_A, (b) (4) using the XTT test with an extract of the test items.

Cell line:	Mouse L929
Negative Control:	RM-C (high density polyethylene) (Lot# C-042) (100% of extract)
Positive Control:	Latex (Lot# 032006944110385) (3-100% of extract)
Medium Control:	Complete medium
Test item:	C08075_A, (b) (4) (3-100% of extract) C08075_A, (b) (4) (3-100% of extract)
Incubation time:	24 hours
Cytotox test:	50 µL XTT mixture added, then absorbance reading at 450 nm

There was no observed difference in absorbance reading between the negative control and medium control, and the positive control showed a distinct dose-related reduction in cell viability and proliferation (XTT_{50} = 20.2%). Absorbance readings for C08075_A, (b) (4) indicated slight cytotoxicity at 100% extract with cell viability reduced to 67.24% (no XTT_{50} value since viability was not reduced to below 50%). C08075_A, (b) (4) were also slightly cytotoxic with cell viability reduced at 70% and 100% extracet (66.94% and 61.90%, respectively; no XTT_{50} value since viability was not reduced to below 50%).did not indicate any cytotoxic effect up to the highest concentration of extract, and an XTT_{50} could not be calculated.

Conclusion: C08075_A, (b) (4) and C08075_A, (b) (4) alone do possess cytotoxic potential.

Study title: Cytotoxicity assay in vitro: Evaluation of materials for medical devices (XTT-test) with LE1002C (extraction period: 72 hours)

Study no.:	T1078925EXT (Report #A51185)
Study report location:	IND 73505; SD #51 (eCTD #45); 8-31-2011
Conducting laboratory and location:	(b) (4)
Date of study initiation:	May 4, 2010
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	LE1002C (Batch #C08069), purity 99.99%. Extracted in 5 mL 0.9% (w/v) NaCl in deionized water, supplemented with 10% FCS, 1% penicillin/streptomycin, and 1.1 g/L glucose (complete saline), for 72 hours. (b) (4)

This in vitro study was performed to assess the cytotoxic potential of LE1002C using the XTT test with an extract of the test items.

Cell line:	Mouse L929
Negative Control:	RM-C (high density polyethylene) (Lot# C-042) (100% of extract)
Positive Control:	Latex (Lot# 12200840820074) (3-100% of extract)
Medium Control:	Complete medium
Solvent Control:	Complete saline
Test item:	LE1002C (3-100% of extract)
Incubation time:	72 hours
Cytotox test:	50 µL XTT mixture added, then absorbance reading at 450 nm

There was no observed difference in absorbance reading between the negative control, medium control, or solvent control, and the positive control showed a distinct dose-related reduction in cell viability and proliferation (XTT_{50} = 19.2%). Absorbance readings for LE1002C indicated cytotoxicity at 70% and 100% extract with cell viability reduced to 9.73% and 1.15% respectively. The calculated XTT_{50} value is 55.2%. No cytotoxicity was observed at lower concentrations.

Conclusion: LE1002C does possess cytotoxic potential.

Study title: Cytotoxicity assay in vitro: Evaluation of materials for medical devices (XTT-test) with LE1002C (extraction period: 28 days)

Study no.:	T2078926EXT (Report #A51186)
Study report location:	IND 73505; SD #51 (eCTD #45); 8-31-2011
Conducting laboratory and location:	(b) (4)
Date of study initiation:	April 30, 2010
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	LE1002C (Batch #C08069), purity 99.99%. Two pieces were extracted in 10 mL 0.9% (w/v) NaCl in deionized water, supplemented with 10% FCS, 1% penicillin/streptomycin, and 1.1 g/L glucose (complete saline), for 28 days. (b) (4)

This in vitro study was performed to assess the cytotoxic potential of LE1002C using the XTT test with an extract of the test item.

Cell line:	Mouse L929
Negative Control:	RM-C (high density polyethylene) (Lot# C-042) (100% of extract)
Positive Control:	Latex (Lot# 12200840820074) (3-100% of extract)
Medium Control:	Complete medium
Solvent Control:	Complete saline
Test item:	LE1002C (3-100% of extract)
Incubation time:	72 hours
Cytotox test:	50 µL XTT mixture added, then absorbance reading at 450 nm

Study report A52522 (not reviewed) validated the cell culture medium concentrations of silver (ZK65223) in this study after extraction for 28 days. Concentrations were as follows:

Sample Name	ZK 65223 [µg/L]
S_L_1347202_d28	< LLOQ
S_K1_1347202_d28	163
S_K2_1347202_d28	428
S_K3_1347202_d28	1186
S_K4_1347202_d28	2695
S_K5_1347202_d28	4066

There was no observed difference in absorbance reading between the solvent control and medium control. The negative control showed a 20% reduction in cell viability (80.94% cell viability), though the report lists no relevant difference from solvent or

medium controls. The positive control showed a distinct dose-related reduction in cell viability and proliferation (XTT_{50} = 6.7%). Absorbance readings for LE1002C indicated slight cytotoxicity at 70% extract (58.89% cell viability), and clear cytotoxicity at 100% extract with cell viability reduced to 11.24%. The calculated XTT_{50} value is 75.6%. No cytotoxicity was observed at lower concentrations.

Conclusion: LE1002C does possess cytotoxic potential.

Study title: Detection of the haemolytic potential of an extract of C08075_A, (b) (4) with human erythrocytes

Study no.:	T5078901EXT (Report #A46674)
Study report location:	IND 73505; SD #51 (eCTD #45); 8-31-2011
Conducting laboratory and location:	(b) (4)
Date of study initiation:	March 11, 2009
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	C08075_A, (b) (4) (Batch #C08136 (b) (4) and C08069(Ag)) extracted in physiological saline (0.9% (w/v) NaCl in deionized water. (b) (4)

This in vitro study was performed to assess the lytic activity of C08075_A, (b) (4) using a haemolysis test with an extract of the test item.

Test system:	Blood sample obtained from donor not receiving medication, erythrocyte pellet collected and resuspended in physiological saline.
Negative Control:	0.9% NaCl (Lot# 18.12.08)
Positive Control:	Deionized water
Test item:	18 (b) (4), complete surface = 85 cm^2 (1-100% of extract) 3 (b) (4) complete surface = 14 cm^2 (1-100% of extract) (6 (b) (4) and 1 (b) (4) were extracted together)
Incubation time:	3 hours
Measurement:	Absorption measured at 530 nm to cover haemolysis.

The positive control showed 100% lytic index. There was no observed difference in absorbance reading or lytic index between the negative control and any extract concentration of C08075_A, (b) (4). No H_{50} value could be calculated since the lytic index was not increased by 50%.

Conclusion: C08075_A, (b) (4) do not induce haemolysis in human erythrocytes.

Study title: LCS / Silver ion release in vitro

Study no.:	Report #A45288
Study report location:	IND 73505; SD #51 (eCTD #45); 8-31-2011
Conducting laboratory and location:	Bayer HealthCare
Date of study initiation:	May 16, 2011
GLP compliance:	No
QA statement:	No
Drug, lot #, and % purity:	Levonorgestrel contraceptive system (LCS) samples from batches C08105 (fresh sample; EO sterilized), C07010 (b) (4) EO sterilized), C10101 (EO sterilized), C10101 (b) (4)

This in vitro study was performed to examine the amount of silver released from LCS samples into physiological saline at various time points following a 28-30 day incubation. The silver profile was added to the vertical stem of the T-body to improve ultrasound detection. The resulting concentration of released silver was determined using inductively coupled plasma mass spectrometry with validated ICP-MS method.

LCS samples sterilized with (b) (4) seemed to release more silver ions than wither aged or fresh samples sterilized with EO. The concentration range of silver released over 30 days was between 99.83 – 293.66 μg/L, with amounts averaging between 1 – 2.94 μg over 28-30 days (0.036 – 0.098 μg/day).

The EPA's established oral reference dose (an estimate of a daily exposure to the human population that is likely to be without an appreciable risk of deleterious effects during a lifetime) is 0.005 mg/kg/day (5 μg/kg/day)[1]. The released silver in this IUS equates to 0.036 – 0.098 μg/day or 0.0006 – 0.0016 μg/kg/day. As a result, the released levels of silver are safe.

[1] http://www.epa.gov/iris/subst/0099.htm

Figure 3: Cumulative concentration of released Ag (averaged)

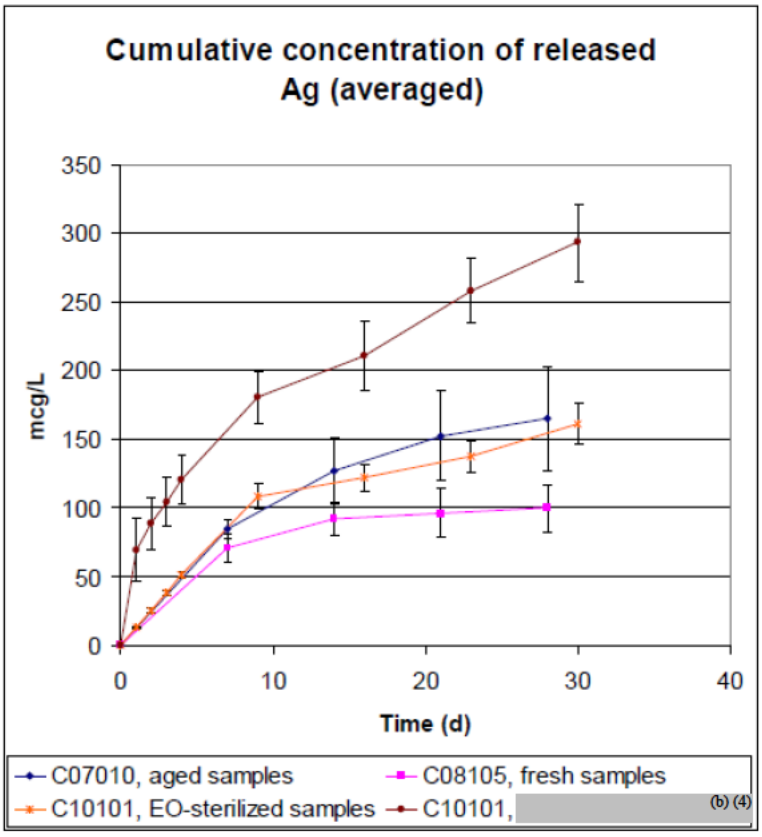


Figure 2 Total cumulative concentration of released silver ion from LCS samples.

11 Integrated Summary and Safety Evaluation

LCS12 (LNG-IUS) is a drug-delivery device designed to be inserted in the uterus, and to release small amounts of levonorgestrel (LNG) over time, conferring its long term contraceptive effect. LCS12 is modeled after the approved IUS product Mirena, but is designed to deliver a lower dose of LNG than Mirena, once inserted. Though LCS12 is comprised of a drug substance and a device, it is regulated as a 'drug product' and not a device. However, evaluation of the safety of both the drug substance and delivery system are necessary. The safety of LNG itself has already been established and is well-documented in the published literature and through over 30 years of clinical use. LNG plus estrogen is the formulation for many oral contraceptives, long-acting LNG is used alone in intrauterine devices (Mirena) and subdermal implants (Norplant and Norplant II), and oral LNG alone is used for emergency contraception (Plan B). Therefore, no studies were conducted by the Sponsor to evaluate the safety of LNG. Components of the T-body and the inserter were evaluated to determine their safety and tolerability during insertion and long-term implantation in the uterine cavity.

A number of acute toxicity, mutagenicity, and tolerability studies were performed on the components of LCS12, along with a chronic 9-month toxicity study where a modified LCS12 was implanted in female monkeys. The 3 components of the inserter (insertion tube, flange and plunger) were well-tolerated following intracutaneous administration, and had no skin sensitization or cytotoxic potential. The inserter poses no safety concerns for clinical use. Intrauterine administration of a modified LCS12 (for size purposes) in the monkey resulted in pharmacologic effects, but no local tolerance or safety issues. Therefore, the LCS12 product itself was deemed safe.

The silver component alone, and/or the (b) (4) products were tolerated with no signs of toxicity based on single i.v., i.p. and i.c. administration in mice and 13 weeks (intrauterine) administration in the monkey; were not irritants via i.m. implantation in the rabbit; exhibited no skin-sensitization potential; do not induce haemolysis in human erythrocytes; and were not mutagenic based on the Ames Test or mouse lymphoma assay.

However, extracts of the silver ring itself, and the (b) (4) do possess slight to clear cytotoxic potential (70-100% extracts). This is not expected to be a concern during clinical use though. A 30% extract was not deemed cytotoxic and the Sponsor reports that the silver concentration in this extract was approximately 6-fold higher than the proposed silver concentration released by the LCS12 product (determined in an *in vitro* release test; ~165 μg/L). Cytotoxic extracts (70% and 100%) were reported by the Sponsor to have silver concentrations 13 and 20 times higher than the concentrations determined in the release test. The Sponsor notes that it is unlikely that such high concentrations of silver ion would be achieved *in vivo* by the silver ring used in LCS12. In addition, no other toxicity, intolerance or mutagenicity was noted, so the use of silver in the LCS12 T-body for ultrasound detection is not a safety concern.

As mentioned above, study report 45288 investigated the LCS12 in vitro silver ion release rate. It was determined that the concentration range of silver released from LCS12 over 30 days was between 99.83 – 293.66 μg/L, with amounts averaging between 1 – 2.94 μg over 28-30 days (0.036 – 0.098 μg/day or 0.0006 – 0.0016 μg/kg/day). The EPA's established oral reference dose (an estimate of a daily exposure to the human population that is likely to be without an appreciable risk of deleterious effects during a lifetime) is 0.005 mg/kg/day (5 μg/kg/day).[2] In addition, published literature documents that the maximum daily intake of silver in a non-occupationally exposed population (via food and drinking water, or inhaled air) is 110 μg/day.[3,4,5] Silver rings weighed from recovered ex vivo samples of LCS12 used in vivo showed that the in

[2] http://www.epa.gov/iris/subst/0099.htm
[3] Holler J, Nordberg GF, Fowler BA (2007). Silver. In: Handbook on the Toxicology of Metals (3rd edition). Nordberg et al, Eds. Academic Press, Inc.
[4] Juberg DR (1997). Health risk assessment of environmental silver. In: Andren, Anders W.; Bober, Thomas W., Eds. The 5th international conference proceedings: transport, fate and effects of silver in the environment [Madison, Wis.]: University of Wisconsin System, Sea Grant Institute.
[5] Fung MC, Bowen DL (1996). Silver products for medical indications: risk-benefit assessment. J Toxicol Clin Toxicol., 34(1):119-126.

vivo release is approximately 100 ng/day during a 3 year usage. In comparison to all of these values, the in vitro released silver in LCS12 (0.036 – 0.098 μg/day or 0.0006 – 0.0016 μg/kg/day) is at least 3000 times lower than the oral reference dose, and 1100 times lower than the population maximum daily intake. The in vivo release derived from ex vivo samples (100 ng/d) is also 1100 times lower than the population maximum daily intake. Even under the assumption that the complete silver ring would dissolve during the intended period of use, the maximum theoretical exposure would be 22 mg/1080 days (20 μg/day), or 5 times less than the population maximum daily intake. As a result, the released levels of silver are safe.

A comparison of the clinical and nonclinical AUC values of LNG reveals appropriate safety margins of exposure. The Phase 2 clinical study (A46796) revealed a clinical $AUC_{0\text{-}Tlast}$ of 85993 ng*d/L for LCS12, and the Phase 3 clinical study (A52238) revealed a clinical $AUC_{0\text{-}Tlast}$ of 76461 ng*d/L for LCS12 (0-Tlast equals from time 0 to the last data point > LLOQ). In the chronic monkey toxicity study, where monkeys were implanted with an IUS with 16 μg/d release rate, PK analysis determined an $AUC_{0\text{-}Tlast}$ of 16893 ng*h/mL, which equates to 703875 ng*d/L. Based on AUC, the 16 μg/d release rate dose in the monkey is 8-9 times higher than the planned LCS12 clinical dose, and was found to have no toxicity or safety issues. In addition, LCS12 is designed similarly to Mirena, but with a lower daily release rate, and smaller size of the system. The safe history of clinical use with Mirena (20 μg/day LNG release) also supports the clinical safety of LCS12 (10 μg/day LNG release).

Nonclinical issues regarding labeling:
The Sponsor's proposed LCS12 (Skyla) labeling is modeled off of the approved physicians labeling for Mirena (Bayer is the Sponsor for both Mirena and Skyla). This reviewer has reviewed Sections 8 and 13 of the label, along with pharmacologic class in Highlights, and has also compared the Mirena and Skyla labels. The Sponsor has proposed minor additions of language to Sections 8.1, 8.3 and 8.4, but these are based on clinical knowledge. All changes to Section 8 appear appropriate, and there are no objections. The Sponsor has added a clarifying statement "…among women using progestin-only birth control pills" to the sentence in section 8.3 "Isolated postmarketing cases of decreased milk production have been reported among women using progestin-only birth control pills", which is different than in the Mirena label. Support for this statement is being discussed with the clinical review team.

The Sponsor has proposed no changes to the language in Section 13 (Carcinogenesis, Mutagenesis, Impairment of Fertility), from that of Mirena, other than the change in dose multiple values. These values are accurate. However, a change in wording is proposed by the review team to conform to the labeling in this Section of oral contraceptive products. Deletion of (b) (4) is proposed, with only a statement referring to the Warnings and Precautions Section 5.8 regarding Breast Cancer. This will also be proposed for Mirena.

The pharmacologic class is incorrect as currently listed in Highlights of Prescribing Information, and should be edited based on the FDA Established Pharmacologic Class

listings. The word (b) (4) should not be used, and while the pharmacologic class listing suggests the use of the term IUD, the term IUS is more appropriate, as this is technically a drug product and not a device.

The following is the Sponsor's proposed labeling (submitted March 2012; eCTD #0005, SD#6) for Highlights, Section 8 and Section 13, with recommended annotated edits to the Highlights section, and Section 13.1 (insertions are underlined, deletions are ~~strikethrough~~):

Highlights of Prescribing Information
Indications and Usage
Skyla is a (b) (4) progestin-containing intrauterine system (IUS) indicated for prevention of pregnancy for up to 3 years (1)

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
The use of Skyla during an existing or suspected pregnancy is contraindicated. Many studies have found no harmful effects on fetal development associated with long-term use of contraceptive doses of oral progestins. The few studies of infant growth and development that have been conducted with progestin-only pills have not demonstrated significant adverse effects. *[See Contraindications (4), Warnings and Precautions (5.1, 5.2).]*

8.3 Nursing Mothers
In general, no adverse effects have been found on breastfeeding performance or on the health, growth, or development of the infant. Isolated postmarketing cases of decreased milk production have been reported (b) (4) . Small amounts of progestins pass into the breast milk of nursing mothers resulting in detectable steroid levels in infant serum. *[See Warnings and Precautions (5.5).]*

8.4 Pediatric Use
Safety and efficacy of Skyla have been established in women of reproductive age. (b) (4) efficacy is expected to be the same for postpubertal (b) (4) under the age of 18 as for users 18 years and older. Use of this product before menarche is not indicated.

13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
[See Warnings and Precautions (5.8).]

(b) (4)

Conclusions: Pharmacology/Toxicology recommends approval for LCS12 (Skyla) for prevention of pregnancy for up to 3 years.

12 Appendix/Attachments

Appendix 1: Nonclinical studies incorporated by reference to NDA 21225

Table 6: Tabular listing of report titles incorporated by reference to NDA 21225

Test item code	Report No	Study title
LE10900D	AX44	PYROGEN TEST IN RABBITS
	AX45	INTRACUTANEOUS TEST IN THE RABBIT
	AX46	MUSCLE IMPLANTTION TEST IN THE RABBIT
	AX47	SYSTEMIC INJECTION TEST IN THE MOUSE
	AX48	THE GUINEA PIG MAXIMIZATION TEST
	AX49	HEMOLYSIS TEST
	AX50	IN VITRO CYTOTOXICITY TEST (USP 2311S0 10993-5 ELUTION TEST)
	AX51	BACTERIAL MUTATION ASSAY
	AX52	L5178Y TK+/- Mouse Lymphoma Mutation Assay
	AX53	LYMPHOCYTE CYTOGENETIC STUDY
	AX54	MOUSE MICRONUCLEUS TEST
LE10200B	AX55	PYROGEN TEST IN RABBITS
	AX56	INTRACUTANEOUS TEST IN THE RABBIT
	AX57	MUSCLE IMPLANTTION TEST IN THE RABBIT
	AX58	SYSTEMIC INJECTION TEST IN THE MOUSE
	AX59	TEST FOR DELAYED CONTACT HYPERSENSITIVITY USING THE GUINEA PIG MAXIMIZATION TEST
	AX60	HEMOLYSIS TEST
	AX61	IN VITRO CYTOTOXICITY TEST
	AX62	BACTERIAL MUTATION ASSAY
	AX63	MOUSE LYMPHOMA MUTATION ASSAY
	AX64	LYMPHOCYTE CYTOGENETIC STUDY
	AX65	MOUSE MICRONUCLEUS TEST
LE11600F	B046	SIX MONTH TOXICITY STUDY IN THE RAT AFTER SUBCUTANEOUS IMPLANTATION
LE11601E	B220	MOUSE MICRONUCLEUS TEST
	B221	IN VITRO MAMMALIAN CHROMOSOME ABERRATI,9PtTg:~t7rPIJ':' HUMAN LYMPHOCYTES
	B222	MAMMALIAN CELL MUTATION ASSAY
	B223	BACTERIAL MUTATION ASSAY
	B224	IN VITRO CYTOTOXICITY TEST USP *23/1S0* 10993-5 ELUTION TEST
	B225	HEMOLYSIS TEST
	B226	TEST FOR DELAYED CONTACT HYPERSENSITIVITY USING THE GUINEA PIG MAXIMIZATION TEST
	B227	SYSTEMIC INJECTION TEST IN THE MOUSE
	B228	MUSCLE IMPLANTATION TEST IN THE RABBIT

Test item code	Report No	Study title
LE11601E	B229	INTRACUTANEOUS TEST IN THE RABBIT
	B230	PYROGEN TEST IN RABBITS
LE11600A/ LE11601A	B180	9 months local and systemic tolerance study in monkeys with an intrauterine system inserted into the uterus, 1999
	B565	Determination of the release rate of levonorgestrel from the test articles used in the study in cynomolgus monkeys, LE116-97101
	B574	Bioanalytical report: Levonorgestrel concentrations in serum and uterine tissue samples of the monkey study LE116-97101, TXST19970167, 9 months local and systemic tolerance study in monkeys with an intrauterine system inserted into the uterus'
LE040902N	A24173	9 months local and systemic tolerance study in monkeys with an intrauterine system inserted into the uterus, 2007
Modified LNG-IUS	B524	EMBRYO/FETAL TOXICITY AND TERATOGENIC POTENTIAL STUDY OF LEVONORGESTREL ADMINISTERED VIA A SILASTIC INTRAUTERINE DEVICE TO PREGNANT NEW ZEALAND WHITE RABBITS

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

/s/

KIMBERLY P HATFIELD
11/21/2012

ALEXANDER W JORDAN
11/23/2012