Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for Levonorgestrel

Proprietary Product Name: Jaydess (intrauterine drug delivery system)

Sponsor: Bayer Australia Ltd

Date of first round CER: 15 December 2012
Date of second round CER: 29 April 2013 (amended 5 May 2013)

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <http://www.tga.gov.au>.

About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

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Contents

List of abbreviations

Abbreviation	Meaning
AE	Adverse event
BMI	Body mass index
CMPH (CHMP)	Committee for Medicinal Products for Human Use formerly known as Committee for Proprietary Medicinal Products - a European Medicines Agency committee
FAS	Full analysis set
FDA	US Food and Drugs Administration
ICH	International Committee on Harmonisation
IUS	Intrauterine Device
IVIVC	*In vitro–In vivo* Correlation
LCS 12	To be marketed as Jaydess in Australia
LNG	levonorgestrel

Abbreviation	Meaning
LCS	Low dose levonorgestrel contraceptive intrauterine systems
PI	Pearl Index
PID	Pelvic Inflammatory Disease
PIP	Paediatric investigation plan
TGA	Therapeutic Goods Administration
SOC	System Organ Class
Wy	Women years

1. Introduction

This is an application to register a new strength (13.5mg) of levonorgestrel for an intrauterine delivery system (Jaydess). There is a 52mg levonorgestrel intrauterine delivery system already registered in Australia (Mirena 52 mg levonorgestrel, AUST R 73027). The approved indication for levonorgestrel is contraception.

The proposed indication is as a low dose levonorgestrel (LNG) intrauterine delivery system for contraception. This is the same indication to Mirena. The wording of the proposed indication [as stated in the clinical overview] is *Contraception for up to 3 years in nulliparous and parous women.*[1]

One Jaydess is inserted into the uterine cavity and is effective for up to three years. It is removed manually and can be removed at any time prior to 3 years.

1.1. Overseas regulatory history

There have been discussions with several overseas regulatory bodies which are documented in the submission. Specifically:

- The Swedish Medical Products Agency (MPA) has been consulted by the Sponsor to discuss aspects of the development program including study endpoints, interim analysis, the inclusion of nulliparous women and the development of an *in vitro*/*in vivo* correlation (IVIVC) prior to start of the Phase 2 and 3 clinical development phase of LCS12 (Jaydess).
- Based on the Phase 2 study results, in early 2010 the Sponsor met with several European health authorities to discuss the proposed modifications of the development programme, specifically the ethylene oxide sterilization and the IVIVC simulations. These include:
  - Sweden: MPA, 22 Mar 2010
  - Germany, Federal Institute for Drugs and Medical Devices (BfArM), 31 May 2010
  - UK: Medicines and Healthcare Products Regulatory Agency (MHRA), 13 Apr 2010

[1] The sponsor initially proposed the indication: *'contraception for up to 3 years'.* At the time the application was accepted for evaluation the sponsor amended the proposed indication to *'contraception'* in line with that approved for Mirena.

- In January and February 2011, the Sponsor met with the following European health authorities for Scientific Advice Meetings in order to seek guidance on the development of a safety risk management plan (RMP) for LCS12 and on the clinical development plan for LCS16 in the indication of heavy menstrual bleeding (LCS12 of relevance in this application)
- Sweden: MPA, 21 Jan 2011
- Germany: BfArM, 25 Jan 2011. One specific aspect of the scientific advice from the BfArM on the RMP (informed consent) was followed up in the form of a Written Scientific Advice, 1 Sep 2011.
- The Netherlands: The Medicines Evaluation Board (MEB), 27 Jan 2011
- UK: MHRA, 1 Feb 2011
- Swedish health authority Aug 2011 to discuss and reach agreement on the content and organization of Bayer's proposed marketing authorisation application in eCTD format.

[Information redacted]

2. Clinical rationale

LNG is one of the 19-nortestosterone progestins. It is used worldwide as the progestin component in oral contraceptives, in hormonal replacement therapy, subdermal implants and intrauterine systems (IUS). Jaydess (LCS12) is a LNG-releasing intrauterine system (IUS) to be used for long-term contraception (up to three years). The dose of LNG released daily from the IUS results in tissue concentrations that make conditions unfavourable for pregnancy by making the endometrium relatively insensitive to circulating estradiol and thickening the cervical mucus preventing fertilization. There is also an inhibitory effect on ovulation which is clinically relevant at higher concentrations than that achieved by Jaydess.

There is already a LNG intrauterine implant available for this indication (Mirena). However compared with the Mirena duration of five years, LCS12 was developed to provide contraceptive protection for a shorter period of time - up to three 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 Mirena. This aims to ensure easier and more acceptable insertion for nulliparous women.

2.1. Guidance

The clinical development program of LCS12 is considered adequate to satisfy the requirements of the CHMP *'Guideline on Clinical Investigation of Steroid Contraceptives in Women'* (EMEA 2005) <http://www.emea.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003349.pdf> (accessed December 15, 2012).

Paediatric guidance: A paediatric investigation plan (PIP) (EMEA-000606-PIP01-09) is in place for LCS12 (Jaydess) that fulfils the [EMA] conditions of Article 30 of Regulation (EC) 1901/2006.

This PIP could potentially provide the basis for a Pediatric Use Marketing Authorization (PUMA) but is not required for this application as the intended use of this product is not for children.

3. Contents of the clinical dossier

3.1. Scope of the clinical dossier

The submission contained the following clinical information:

- **Module 1**

Letter of application, administrative information and prescribing information, certification in relation to patents, provisional records summary, application form, proposed Australian Product Information and package insert, information about the experts – quality, clinical, non clinical; GMP clearance letters for all overseas manufacturing sites, declaration of compliance with pre-submission planning form and planning letter, statement on availability of individual patient data, data-set similarities and differences, information on overseas regulatory studies, justification for not providing appropriate biopharmaceutic studies, references to paediatric development program, EU Risk Management Plan.

- **Module 2**

Introduction, Quality Overall Summary (Appendices, Pharmaceutical Documentation, Introduction to the Quality Overall Summary, Quality Overall Summary on the Pharmaceutical Documentation Module), non-clinical overview, clinical overview, non clinical summary, pharmacokinetics tabulated summary, toxicology tabulated summary, toxicology written summary and Table of Contents.

- **Module 5**
  - 2 Reports of Biopharmaceutical Studies – *In vitro–In vivo* Correlation Study Reports
  - 12 Reports of Biopharmaceutical Studies –Bioanalytical and Analytical Methods for Human Subjects
  - 2 studies pertinent to pharmacokinetics Using Human Biomaterials – Plasma Protein Binding Study Report and Hepatic Metabolism and Drug Interaction Study
  - 2 Reports of Human Pharmacokinetic Studies – Healthy Subject PK and Initial Tolerability Study and Patient PK and Initial Tolerability Study Reports
  - 3 Reports of Human Pharmacokinetic Studies – Population PK Study Reports
  - 2 Report of Efficacy and Safety Studies – Controlled Clinical Studies Pertinent to the Indication and Uncontrolled Clinical Studies Pertinent to the Indication
  - 7 Other Study Reports/Protocols

3.2. Paediatric data

The PI proposes use in age 18 and over.

3.3. Good clinical practice

[Information redacted]

The pivotal and supporting clinical studies A46796 and A52238 are in line with international guidelines on the development of steroid contraceptives in women (1) and have been discussed with several health authorities in Europe and the US Food and Drug Administration (FDA).

The documentation provided in the submission shows that all clinical studies performed in the framework of this submission were or are being conducted in accordance with the International Conference on Harmonization (ICH) Good Clinical Practice, the principles of the Declaration of Helsinki, and all applicable national regulations valid at the time the studies were performed. The protocols and protocol amendments were reviewed and approved by Independent Ethics Committees or Institutional Review Boards.

Additionally it should be noted that because the product consists of various different plastic materials as well as an active drug, the nonclinical testing strategy for LCS12 (Jaydess) considered both the conventional drug development regulatory requirements as well as those applicable for development of medical devices.

4. Pharmacokinetics

4.1. Studies providing pharmacokinetic data

Two doses of low dose LNG - LCS12 (Jaydess) and LCS16 were investigated in a Phase 2 and a 3 study. The formulations of these doses were very similar.

4.1.1. Models and simulation PK studies (IVIVC model development)

As LCS12 and LCS16 are used for a long period of time (3 years), a short-term standard bioavailability study to characterize the formulations was difficult. Instead an *in vitro* dissolution method was developed to describe the *in vivo* behaviour of LCS12 and LCS16 over the anticipated time of IUS use. The long-term *in vitro* dissolution data was from the same batches that were used in the clinical phase 2 study A46796 and the phase 3 study A52238. This *in vitro* dissolution testing of Jaydess used in the clinical studies revealed a fast decline in rate of release during the first four weeks from approximately 25 µg/day around day 2-14 µg/day for the sampling period days 5-11, and 12 µg/day for the sampling period days 19-25. 6 months later the *in vitro* release rate was around 8 µg/day and declined to around 5 µg/day at the end of year 3.

The *in vivo* release rate was determined by this *in vitro* dissolution data and analysis of the *ex vivo* residual content of LNG in Jaydess samples taken from women who prematurely discontinued the study or finished the study as planned after approximately 3 years in two clinical trials. About 100 *ex vivo* samples of Jaydess were analysed from the Phase 2 study and about 800 samples from the Phase 3. The biopharmaceutical characterisation of Jaydess was focused on *in vitro* data obtained over the intended period of use and on *ex vivo* residual content analyses, to provide information on local LNG release rates concentrations (as opposed to serum LNG concentrations).Although the FDA and CHMP Guidance discuss requirements for non-intrauterine dosage forms only, these FDA/CHMP Guidelines were used for development and validation of an IVIVC for LCS.

Table 1. Calculated *in vivo* release rates of LNG [µg/day]

Calculated *in vivo* release rates of LNG [µg/day] in LCS12 at time points during the 3-year period based on the *ex vivo* residual content data from the phase 3 study A52238. These are model values and not human.	
Release rate after 24 days, i.e. on day 25	14.0

Calculated *in vivo* release rates of LNG [µg/day] in LCS12 at time points during the 3-year period based on the *ex vivo* residual content data from the phase 3 study A52238. These are model values and not human.	
Release rate after 60 days	9.6
Release rate after 3 years	5.4
Average release rate over 3 y	6.4

In both Phase 2 (A46796) and Phase 3 (A52238) studies, a subset of 12 women per treatment arm was included to determine non-compartmental pharmacokinetic parameters of LNG after both LCS12 and LCS16 insertion. In A52238 a population pharmacokinetic analysis was conducted using serum concentration data of LNG and SHBG from all women who were treated with LCS12 or 16. This data was also used in the planning of the post-menarche study (14371).

4.1.1.1. A46796

4.1.1.1.1. Pharmacokinetic / pharmacodynamic results

In a subgroup (n= 12-13 subjects per treatment), blood samples were taken on a regular basis to determine the concentration of LNG and SHBG in serum. Specifically, Serum LNG and SHBG were determined at baseline and at day 1, 3 and 7 and 2 weeks after start of treatment. Thereafter, they were determined at every visit. One day after insertion (first blood sampling point) measurable serum levels of LNG were already observed in all subjects. Mean pharmacokinetic parameters of LNG of this subset (subset 3) observed after insertion of LCS12, LCS16 and Mirena are as below. The geometric mean with the geometric coefficient of variation (CV, in parentheses) are given; for tmax the median and the range (in parentheses) are provided.

Table 2. Levonorgestrel pharmacokinetic parameters. Geometric mean (geometric coefficient of variation (CV) or (for tmax) median (range).

	Cmax(ng/L)	tmax (d)	Cav (ng/L)
LCS12	137 (28.6%) (N=12)	14 (1-379) (N=12)	78.3 (31.4%) (N=8)
LCS16	186 (46.9%) (N=12)	11 (2-49) (N=12)	106 (55.1%) (N=7)
Mirena	360 (45.9%) (N=13)	7 (3-927) (N=13)	218 (35.2%) (N=12)

Table 3. Levonorgestrel concentrations. Geometric mean (geometric CV)

	C(6)(ng/L)	C(12)(ng/L)	C(24)(ng/L)	C(36)(ng/L)
LCS12	93.3 (38.7%) N=12	83.3 (23.5%) N=12	65.7 (31.7%) N=9	68.5 (33.0%) N=8
LCS16	121 (53.1%) N=10	109 (44.0%) N=9	98.9 (64.9%) N=7	85.2 (63.9%) N=7
Mirena	254 (38.0%) N=13	222 (40.4%) N=12	192 (36.9%) N=12	165 (40.5%) N=12

Cmax = maximum observed concentration; tmax = time to reach Cmax; Cav = average steady state concentration (AUC(0-tlast)/ tlast); C(6) = observed concentration at 6 month after insertion; C(12) = observed

concentration at 12 month after insertion; C(24) = observed concentration at 24 month after insertion; C(36) = observed concentration at 36 month after insertion

After insertion of LCS12, a geometric mean maximum concentration of LNG of 137 ng/L was reached after 14 days (median). After insertion of LCS16, the corresponding values were 186 ng/L after 11 days. Thereafter, serum levels of LNG declined slowly to mean values of 69 ng/L, 85 ng/L and 165 ng/L at the end of the observation, 36 months after insertion of LCS12, LCS16 and Mirena, respectively. There was high variability of the individual serum concentrations, resulting in difficulty calculating the half-life.

4.1.1.2. A52238

4.1.1.2.1. Pharmacokinetic (PK) evaluation

The population PK/PK model developed based on the phase II study 308901 was applied to the data from A52238. The covariate analysis, performed on all data, revealed an effect of body weight on the clearance parameter (range 39 to 160 kg, N=2547). The change of the clearance value per kg was approximately 1.6% of the typical value. This means that a woman with a body weight of 39 kg would have a clearance value of 57% compared to a typical woman with a median body weight of 66.0 kg. A clearance value of 249% of the typical clearance would be expected in women weighing around 160 kg. If SHBG wasn't different between lean and obese, this would mean a 1.75-fold higher concentration in a woman weighing 39 kg and a 2.5-fold lower concentration in a woman weighing 160 kg in comparison to the typical concentrations presented. 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. This is an important point as there were not many women meeting the MedRA criteria for obesity (n=2 (0.1%) in the LCS12 and n=1 (<0.1%) in the LCS16). In the clinical studies, there were 17% (A52238) and 7.5 % (A46796) of women who were in the BMI>30kg/m^2 group, although as the PI was relatively low, assessing a reduced effect in the obese population as compared to the lean was unable to be undertaken. Further, in the 'inclusion' criteria for the study, women had to be judged as 'healthy' and also without hypertension.

4.1.1.2.2. Non-compartmental evaluation of subset 3 (subgroup of A52238)

Mean PK parameters of LNG in subset 3 observed after insertion of LCS12 and LCS16 are shown below with mean and coefficient of variation (CV, in parentheses) and the median and the range (in parentheses) are provided.

Table 4. Mean pharmacokinetic parameters of LNG observed after insertion of LCS12 and LCS16 (N=7 LCS12, N=6 LCS16)

	AUC(ng·d/L)	Cmax (ng/L)	tmax (d)	Cav (ng/L)
LCS12	76461 (41.6%)	171 (52.1%)	2.00 (1.00-16.0)	70.0 (42.3%)
LCS16	136358 (53.9%)	264 (62.5%)	7.50 (3.00-364)	125 (54.0%)

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

This data was used to determine the *in vivo* LNG release rate. Based on LNG in vitro release rates and *ex vivo* LNG residual content analyses, the in vivo LNG release rates of LCS12 and LCS16 at the beginning, the end and on average during treatment are:

Table 5. Calculated *in vivo* release rates at the beginning, end and average during LCS12/LCS16 use (µg/day).

Parameter	*In vivo* release LCS12	*In vivo* release LCS16
Early release (7-d, d 19-25)	10.0	14.9
Average release over 3 years	6.4	9.6
Release at the end of 3 years	4.8	7.4

4.1.2. Pharmacokinetic studies

Table 6. Submitted pharmacokinetic studies.

PK topic	Subtopic	Study ID	Description
PK in healthy adults	General PK-Single dose	A229 (note oral LNG) A10982 (note Mirena)	Absolute bioavailability of levonorgestrel from MICROLUT and dose linearity of levonorgestrel pharmacokinetics in 18 healthy, young women A Multicenter, Open-Label, Non-Randomized Study of SHG 00650 Levonorgestrel Intrauterine System in Parous Women Seeking Contraception to Evaluate its Efficacy, Safety, and Pharmacokinetic Profile when Inserted for 12 months
	Multi-dose	N/A	
	Bioequivalence† - Single dose	13362 13363	There was no pharmacokinetic bioequivalence data provided. These 2 studies were to show pharmacodynamic equivalence with other contraceptives and dose comparison with other LNG formulations.
	Multi-dose	None provided	
	Food effect	Not provided	
PK in special populations	Target population §-Single dose	A46796 (Phase II) – nulliparous AND	Multi-center, open, randomized, dose finding phase II study to investigate for a maximum of three years ultra low dose levonorgestrel contraceptive intrauterine systems releasing *in vitro*

PK topic	Subtopic	Study ID	Description
		parous Target population A52238 (Phase III) 91775 – Phase 3b extension study for A52238 in Asia-Pacific region (China, Korea, Australia)	12 µg/24 h and 16 µg/24 hof LNG compared to MIRENA in nulliparous and parous women in need of contraception A52238 Phase III Multi-center, open-label, randomized study to assess the safety and contraceptive efficacy of two doses (*in vitro* 12µg/24 h and 16µg/24 h) of the ultra low dose levonorgestrel contraceptive intrauterine systems (LCS) for maximum of 3 years in women 18 to 35 years of age and extension phase of the 16µg/24 h dose group (LCS16) up to 5 years Multi-center, open label, single arm study to assess efficacy, safety, bleeding pattern and pharmacokinetics of the ultra low dose levonorgestrel intrauterine contraceptive system (LCS) for a maximum of 3 years in women 18 to 40 years of age
	Multi-dose	Nil Studies	
	Hepatic impairment	A02495	*In vitro* study
	Renal impairment		Not provided
	Neonates/ infants/children/adolescents	14371 (paediatric clinical trial under way for women post menarche)	Not relevant currently for this application if <18 years Multi-center, single-arm study to assess the safety, efficacy, discontinuation rate and pharmacokinetics of the low-dose levonorgestrel intrauterine contraceptive system (LCS12) in post-menarcheal female adolescents under 18 years of age for 1 year, and an optional 2-year extension phase simulations to be confirmed by a population-based sparse sampling approach

PK topic	Subtopic	Study ID	Description
	Elderly		Not relevant for this application
	Paediatrics	A57120	PK population study-Paediatric Scaling LNG LCS IUD (population analysis)
Genetic / gender - related PK	Males vs. females		Females only
PK interactions	LNG		This information was not provided for evaluation Discussions about potential CYP450 3A4 interactions were discussed
Population PK analyses	Healthy subjects	A57120 A57551 (308901) A57552 (310442)	PBPK study-Pediatric Scaling LNG LCS IUD Exploratory population pharmacokinetic analysis of levonorgestrel in the multi-center, open, randomized, dose finding phase II study to investigate for a maximum of three years ultra low dose levonorgestrel contraceptive intrauterine systems Exploratory population pharmacokinetic analysis of levonorgestrel in the multi-center, open-label, randomized phase III study to assess the safety and contraceptive efficacy of two doses
	Target population		These are also the population in the 'healthy' study groups
	Other		

None of the pharmacokinetic studies had deficiencies that excluded their results from consideration.

4.2. Summary of pharmacokinetics

The information in the following summary is derived from conventional pharmacokinetic studies unless otherwise stated. Specifically, standard *in vivo* biopharmaceutical studies have not been conducted. However some pharmacokinetic analysis was performed in small subsets of the 2 large trials. Specifically, in both the pivotal Phase 2 (A46796) and Phase 3 (A52238)

studies, parameters from a subset of 12 women per treatment arm (LCS12 and LCS16) were used to determine a non-compartmental population pharmacokinetic model. In A52238 a population pharmacokinetic analysis was conducted using serum concentration data of LNG and SHBG from all women who were treated with LCS12 or 16. These PK models were used as the basis for understanding relationships between pharmacokinetic and PD variables such as bone mineral density, endometrial pathology, hypothalamic-pituitary function, menstrual cycles and bleeding. In an additional subset of 20 women per treatment arm, other PD parameters including ovarian and cervical effects were investigated.

4.2.1. Pharmacokinetics in healthy subjects

4.2.1.1. Absorption

4.2.1.1.1. Sites and mechanisms of absorption

As described in Section 4.1.1, small subgroups of the large clinical studies of healthy subjects A46796 and A52238, blood sampling for LNG and SHBG concentrations was undertaken to determine pharmacokinetic parameters. Serum concentrations of LNG were detectable one hour after insertion at about one third of the concentration measured after one day for Mirena. Serum Cmax was achieved between 2-14 days after insertion, with a LNG concentration of 137ng/L (Phase 2 study) and 171ng/L (Phase 3 study) with LCS12 and which decreased slowly to mean values in the range of 68 to 69 ng/L (LCS12) after 3 years in the phase 2 and phase 3 studies. Using in addition sparse blood samples with subsequent LNG and SHBG serum analysis from all women that were included, a population pharmacokinetic model was established - typical serum concentrations of LNG from this PK analysis are summarized presented below.

Table 7. Geometric mean, 5th and 95th percentile of LNG serum concentrations post LCS12 insertion (ng/L)

Parameter	1 day (d)	7 d	30 d	3 month	1 year	2 years	3 years
Mean	116	162	131	99.8	71.0	64.3	58.6
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

4.2.1.2. Bioavailability

Typical *in vivo* biopharmaceutical studies, such as a bioavailability or a bioequivalence study, have not been conducted for this application to register Jaydess. From the applicant's point of view this is justified by Jaydess being a mainly locally acting product with low systemic concentrations of LNG in serum (around 100ng/L after 3 months). This compares with concentrations of LNG after daily oral administration of a combined oral contraceptive containing 100 µg LNG of about 4500 ng/L. This 35 fold lower systemic exposure means it is unlikely new safety issues with LNG will be seen with LCS. This is confirmed with a relative lack of activity on ovulation, as compared to the higher dose used in Mirena. It is thus the local release rates of LNG which are important, and the IVIVC model has focused on this using *ex vivo* release rates as confirmation of the model simulation data.

Having mentioned that, in the submission, there is some data on bioavailability provided (Study A229- Absolute bioavailability of levonorgestrel from MICROLUT and dose linearity of levonorgestrel pharmacokinetics in 18 healthy, young women and patient-pk-and-initial-tolerability-study-reports). This is a study completed in 1994 which aimed to determine the

absolute bioavailability after oral administration of three tablets of Microlut (LNG) compared to an intravenous solution of 0.09mg LNG in a mixed micelles solution. Here dose linearity was also measured by administering two further single oral doses of LNG at 0.03mg and 0.27mg (9 tablets).

Thus there were 4 groups in this study:

- Group A – 0.03 mg LNG
- Group B – 0.09 mg LNG
- Group C – 0.27 mg LNG
- Group D – 0.03 mg LNG (intravenous)

Absolute bioavailability was calculated from Treatment B and was 82 +/- 16%. Dose linearity and dose proportionality of LNG PK was seen. No indication of saturable PK was seen; mean clearance from plasma was t1/2 was 20 h. Total clearance was 1 ml/min/kg.

Although LNG in the Jaydess preparation is not administered orally, the information from A229 is helpful for this submission is that it gives guidance in terms of likely distribution after intrauterine insertion, and safety data on serum concentrations over 30 fold higher from oral usage than that with Jaydess. As such, the Sponsor has requested that typical *in vivo* biopharmaceutical studies (e.g. bioavailability or a bioequivalence studies do not need to be undertaken for this application to register Jaydess). It is specifically stated in the submission, serum concentrations of LNG after insertion of Jaydess are below 121 ng/L whereas typical maximum concentrations of LNG after daily oral administration of a combined oral contraceptive containing 100 µg LNG are approximately 4500 ng/L. The Sponsor also argues that the clinical studies suggest that systemic effects from IUS LNG are not clinically significant, and therefore support the absence of *in vivo* biopharmaceutical studies.

4.2.1.2.1. Absolute bioavailability

This information is covered above in 4.2.1.2

4.2.1.2.2. Bioavailability relative to an oral solution or micronised suspension

This information is covered above in 4.2.1.2. Essentially the serum concentrations attained from LCS12 (Jaydess) are log-fold less than that attained with the standard LNG containing oral contraceptive.

4.2.1.2.3. Bioequivalence of clinical trial and market formulations

The formulations of LCS12 and LCS16 used in the clinical studies of phase 2 (A46796) and of phase 3 (A52238) were comparable. Specifically, the drug-containing reservoir was identically composed for the four formulations used in these two trials. There were some modifications to the formulations going from Phase 2 to Phase 3 (the addition of the silver profile and changes in design of the T-body, and for the ongoing Phase 3b studies further modifications of the T-body, the removal thread and the inserter were implemented) but these are not related to the hormone-containing elastomer core. Further, using the *ex vivo* release rate data does not appear to have impacted on the release rates of LNG from the IUS.

4.2.1.2.4. Bioequivalence of different dosage forms and strengths

There were no clinical studies provided examining bioequivalence of difference dosage forms and strengths of Jaydess, however there were comparative studies (A46796) provided comparing different dosages of intrauterine LNG (LCS12, LCS16 and Mirena). Studies 13362 and 13363 were designed to show pharmacodynamic equivalence with other contraceptives and dose comparison with other LNG dosages. In addition, the PK modelling and simulation provides guidance on expected concentrations.

4.2.1.2.5. Bioequivalence to relevant registered products

The only currently registered product that consists of an intrauterine system with LNG is Mirena. Mirena is intended for 5 year use, and contains 52mg LNG. This is four times as high a dose as Jaydess.

4.2.1.2.6. Influence of food

There is no information on the submission for this area but as the drug is given intrauterine, the likelihood of a food interaction is low.

4.2.1.2.7. Dose proportionality

Dose proportionality data on either efficacy or side effects was not easily accessible in this application. However, comparing the contraceptive efficacy of LCS12 (Jaydess) with LCS16 and Mirena showed similar outcomes despite the three formulations investigated in the phase 2 study A46796 showing an increase in the systemic exposure in the order LCS12 (Jaydess) LCS16 and Mirena. Importantly, there was no difference in the effect on the endometrium or on the cervix observed in the phase 2 study between these formulations, although the increasing rate of anovulation for Mirena is likely to be due to the higher average serum concentration of LNG e.g. the respective average LNG serum concentration (Cav), determined in the pharmacokinetic evaluation, amounted to 78.3 ng/L (geometric mean coefficient of variation [CV] 31.4%) for the LCS12 group, to 106 ng/L (geometric mean CV 55.1%) in the LCS16 group and to 218 ng/L (geometric mean CV 35.2%) for Mirena.

4.2.1.2.8. Bioavailability during multiple-dosing

A specific exploratory population pharmacokinetic analysis of LNG in the multi-center, open-label, randomized phase III study was undertaken to assess the safety and contraceptive efficacy of two doses (A57552). However, there was no data provided on multiple sequential dosing.

4.2.1.2.9. Effect of administration timing

Jaydess is to be inserted into the uterine cavity within seven days of the onset of menstruation. It can be replaced by a new system at any time in the cycle. It is stated that Jaydess can also be inserted immediately after first trimester abortion although “End of last pregnancy; vaginal delivery less than 12 weeks, cesarean delivery less than 12 weeks or abortion within 12 weeks immediately before screening” were an exclusion criteria in A46796. “Vaginal delivery, cesarean delivery, or abortion within 6 weeks prior to visit 1” was an exclusion criterion in A52238. There was a reference in the CSR of A46796 to administration post-abortion although it was published in 1982 (Heikkila M, Lahteenmaki P, Luukkainen T. Immediate post-abortion insertion of a levonorgestrel releasing IUD. Contraception 1982; 26,3: 245-59.). Although recent infected abortion is noted as a contraindication in the proposed PI, the PI states that Jaydess can also be inserted immediately after first trimester abortion.

4.2.1.3. Distribution

4.2.1.3.1. Volume of distribution

Levonorgestrel is highly bound with less than 2% circulating as free steroid. It binds non-specifically to serum albumin and specifically to SHBG. The mean apparent volume of distribution of levonorgestrel is approximately 106 L.

4.2.1.3.2. Plasma protein binding

LNG is highly protein bound, predominantly to SHBG (to which it binds with high affinity) and albumin. Changes in the concentration of SHBG in serum therefore result in modifications of the proportions available as free or protein-bound drug, and lead to an increase (at higher SHBG concentrations) or to a decrease (at lower SHBG concentrations) of the total LNG concentration in serum. The magnitude of the decreasing effect of LNG on SHBG is dose dependent.

Following insertion of LCS12 in the Phase 2 study (A46796), SHBG concentrations declined by approximately 16 to 25% during the first 30 days after insertion, reached a plateau and returned to baseline over the three years. In the phase 3 study (A52238), the maximum decline of SHBG concentrations within 18 months was about 33% compared to the pre-dose levels after insertion of LCS12. After 36 months, serum concentrations returned to baseline. The clinical relevance of changes in SHBG or albumin concentrations (which account for approximately 50% of the protein binding each) is unknown, however as with many similar drugs that are highly protein bound, a lower SHBG/albumin leads to less total amount of bound drug, a temporarily higher free drug, which has a higher fraction cleared and thus after several half lives the same free (active) concentration but lower total concentration. There was also significant inter-individual variability in SHBG concentrations noted, but there was no evidence of a clinical effect from this.

4.2.1.3.3. Erythrocyte distribution

This was not presented in the submission and unlikely to be clinically relevant

4.2.1.3.4. Tissue distribution

No studies on LNG tissue concentrations whilst on LCS have been conducted. However, LNG is highly protein bound (>98%), mainly either to albumin or to SHBG in serum. Concentrations in relevant tissue such as endometrium, myometrium, and oviduct tissue have been compared in fertile women using an experimental LNG-IUS with an initial release of 30 µg/day for 4 weeks to those with oral administration of 250 µg LNG alone. In the endometrium where most of the contraceptive effects are seen, 808 ± 511 ng/g wet tissue was found in the IUS-treated subjects versus 3.5 ng/g wet tissue in the orally treated subjects. In the myometrium and oviduct, similar amounts of LNG were measured in both groups (between 1 to 5 ng/g), after both IUS insertion and oral treatment (Nilsson et al. 1982). Although LCS releases less than a half the amount of LNG than in this study, it is likely that tissue distribution in the most clinically relevant tissues is higher and in less clinically relevant tissues, less than that after oral administration of 250ug.

4.2.1.4. Metabolism

4.2.1.4.1. Interconversion between enantiomers

Levonorgestrel is the biologically active enantiomer of norgestrel but is metabolised rather than interconverted as described in 4.2.1.4.2.

4.2.1.4.2. Sites of metabolism and mechanisms / enzyme systems involved

Metabolism of LNG occurs predominantly in the liver by reduction of the Δ4-3-oxo group and hydroxylations at positions 2α, 1β and 16β, followed by conjugation, by CYP3A4. Most of the metabolites that circulate in the blood are sulfates of 3α, 5β-tetrahydro-LNG. These metabolites are not known to be active. Excretion occurs predominantly in the form of glucuronides. Some of the parent LNG also circulates as the 17β-sulfate.

In vitro studies have demonstrated that oxidative metabolism of LNG is catalysed by CYP enzymes, especially CYP3A4 (Study A02495). Thus, drugs which induce or inhibit the activity of CYP3A4 may change the pharmacokinetics of LNG such as anticonvulsants (e.g. phenobarbital, phenytoin, carbamazepine, and possibly also felbamate, oxcarbazepine and topiramate) and anti-infectives (e.g. rifampicin, rifabutin, nevirapine, efavirenz, and possibly griseofulvin) perhaps lowering the serum concentrations of LNG during parallel treatment. Similarly, metabolic activity of CYP3A4 may be strongly inhibited by protease inhibitors such as azole antifungals and some calcium channel blockers.

The influence of these drugs on the efficacy of LCS is not known, but theoretically the clinical effect is likely to be small due to the primarily local mechanism of action and because first pass metabolism is not significant.

However, for the purposes of investigation, the inhibitory potential of LNG on the metabolism of substrates of CYP450 enzymes has been investigated *in vitro* in human liver microsomes. Here the metabolism of testosterone as a model substrate of CYP3A4 was inhibited with a half maximal inhibitory concentration (IC50) of 14-18 µM (A02495). Maximum therapeutic serum concentrations of LNG in humans following oral administration are about 20 nM, much lower than the IC50. Further as maximum serum concentrations after LCS12 insertion are about 170 ng/L - about 0.5 nM or 1/40th lower than the oral concentration, an interaction of LNG with co-administered drugs which are mainly metabolised by CYP3A4 is thus unlikely to be of clinical relevance.

The metabolism of the other model substrates of CYP1A2, 2A6, 2C9, 2C19, 2D6 and 2E1 *in vitro* was not affected.

4.2.1.4.3. Non-renal clearance

Non-renal clearance is via biliary excretion into the faeces. The amount of unchanged non-renal clearance is small as almost all of LNG is metabolised. Non-renal clearance of metabolites is also small. For example with intravenous administration of 0.09 mg LNG to healthy volunteers only trace amounts of LNG are excreted in unchanged form. The metabolites are excreted with faeces and urine with a half-life of about 1 day.

It should be noted that this clearance is following the intravenous administration route. However an older (1994) study provided in the submission (A229 examining bioavailability of LNG) showed that elimination from serum is 20 hours (mean) regardless of whether it is given intravenously or orally. However over 95% of radioactivity was recovered within 8 days after oral administration of radioactively labeled LNG, suggesting that that clearance via the faecal and urine route is about around 75% of the intravenous route.

4.2.1.4.4. Metabolites identified in humans

- Active metabolites

The metabolites have not been shown to be active.

- Other metabolites

Most of the metabolites that circulate in the blood are sulfates of 3α, 5β-tetrahydro-LNG and glucuronides. Some of the parent LNG also circulates as the 17β-sulfate.

4.2.1.4.5. Pharmacokinetics of metabolites

Not relevant.

4.2.1.4.6. Consequences of genetic polymorphism

In vitro studies presented in the submission have demonstrated that oxidative metabolism of LNG is catalysed by CYP enzymes, predominantly CYP3A4 (A02495). CYP3A4 is not polymorphic although there is a population distribution regarding gene activity which could produce changes in clinical concentrations for the same dose across a population. However any pharmacodynamic effect from this was not seen in the pivotal studies.

4.2.1.5. Excretion

4.2.1.5.1. Routes and mechanisms of excretion

The predominant excretion route for LNG is faeces and urine for the metabolites. Almost all the parent is metabolised.

4.2.1.5.2. Mass balance studies

No mass balance studies were provided with this application. However after oral administration of 3H-LNG (0.25 mg, in combination with ethinylestradiol), approximately 95% of radioactivity was recovered within 8 days after administration.

4.2.1.5.3. Renal clearance

There is only a very small amount of LNG excreted unchanged.

4.2.1.6. Intra- and inter-individual variability of pharmacokinetics and pharmacodynamics

PK. There is large intra and inter-individual variability of pharmacokinetics. This is seen in the PK studies, and in addition in the modelled population studies and is covered in Section 4 above.

PD. In 52238 the estradiol (E2) and progesterone (PG) hormone peaks and average concentrations were calculated from samples which were taken twice a week for 6 weeks each year. Mean maximum concentrations for E2 showed high variability with variation from 275.09 pg/mL (SD 132.38 pg/mL; year 1) to 304.59 pg/mL (SD 112.16 pg/mL; year 2) in the LCS12 group. In the LCS16 group, the mean Cmax values varied from 246.16 pg/mL (SD 95.09 pg/mL; year 2) to 300.91 pg/mL (SD 91.54 pg/mL; year 1). In addition, ranges for individual Cmax values varied widely: from a minimum of 62.9 pg/mL (LCS12, year 1) to 500.3 pg/mL (LCS12, years 1, 2, and LCS16, year 1). Similar to the maximum values, the mean average values (Cav) also showed high variability, varying between 93.76 pg/mL (SD 20.05 pg/mL; LCS16, second year) and 121.60 pg/mL (SD 47.55 pg/mL; LCS12 third year).

PG concentrations also showed large inter and intra patient variability – the clinical relevance of which is not clear.

4.2.2. Pharmacokinetics in the target population

It has been shown that dose-proportionality of LNG pharmacokinetics is observed after single oral administration of doses between 30 and 270 µg LNG (the relevant IUS dose) (A229), although the pharmacokinetics will differ with intrauterine absorption.

The pharmacokinetics of LNG also appear to change over time, due to changes in dose (exposure) with time. Most of this is due to the decrease in release of LNG, but in addition there is a dose –dependent effect on SHBG concentrations which may affect the clearance, if only temporarily. The evidence however suggests that pharmacokinetics changes to LNG are small and not likely to be clinically relevant (3).

In the PK substudy of the pivotal studies, a single serum sample for LNG/SHBG per subject was taken at one of visits 3 – 10.

4.2.3. Pharmacokinetics in other special populations

4.2.3.1. Hepatic and renal function

Although there is no data available, pharmacokinetics in subjects with impaired hepatic or renal function are unlikely to be clinically relevant due to small systemic concentrations and mechanism of effect predominantly a local one.

4.2.3.2. Pharmacokinetics according to age

This product is for use in women requiring contraception and as such will not be used for women at the extremes of age.

4.2.3.3. Pharmacokinetics related to genetic factors

Not clinically relevant.

4.2.3.4. Pharmacokinetics in breast feeding

Breast-feeding women is one group where the pharmacokinetics of LNG compounds are of potential clinical importance. In these cases and in the absence of clinical studies, weighted average maternal dose transfer to child can be used to estimate likely ingestion. However, the transfer of LNG from the maternal plasma via breast milk to the infant has actually been studied after insertion of an LNG-containing IUS initially releasing 20 µg/day of LNG (higher release rate

than Jaydess). The study revealed a LNG percentage transfer from maternal serum to breast milk of about 12% and higher percentage LNG transfer from breast milk to infant's serum - about 75% (of the amount in the 12%, or about 8% in total). An arbitrary cut-off of 10% has been selected as a guide to the safe use of drugs during lactation (4). In another study, two LNG-releasing IUSs, one releasing 10 µg/day, the other 30 µg/day, were used. There was no clear difference in the maternal plasma and milk concentrations between the two dose groups. For the 30µg dose group, the total amount of LNG excreted per day in 600 mL breast milk was calculated to be approximately 0.1% of the daily dose (5). A recent Cochrane Review (6) has concluded that the evidence suggests that the LNG-20 IUS (higher release rate than Jaydess) does not impact upon breastfeeding performance or the growth and development of breastfed infants in lactating women. The PI states that "there appears to be no deleterious effect on infant growth or development when using any progestogen-only method after six weeks postpartum. An LNG-IUS does not affect the quantity or quality of breast milk. Small amounts of progestogen (about 0.1 % of the levonorgestrel dose) pass into the breast milk in nursing mothers". This is appropriate for the evidence.

4.2.4. Pharmacokinetic interactions

4.2.4.1. Pharmacokinetic interactions demonstrated in human studies

None demonstrated.

4.2.4.2. Clinical implications of in vitro findings

The *in vitro* findings suggest that drug interactions and inter-patient variability are likely to have some effects on LNG concentrations but little clinical effects. Studies on patients with hepatic or renal impairment have not been done, although these conditions are relatively uncommon in this patient group.

4.3. Evaluator's overall conclusions on pharmacokinetics

LCS12 acts primarily via local effects on the endometrium and cervix therefore systemic concentrations, drug interactions, pharmacogenetic factors and food are of less relevance than for oral administration of LNG such as in oral contraceptives. Further the systemic concentrations are >30 fold more with oral contraceptive use than with the LNG IUS.

There appears to be no pharmacokinetic issues of concern in healthy fertile women as studied in the large trials and there are no further pharmacokinetic studies that need to be undertaken for the requested indication. However, clinical studies have not been undertaken in women in 'special groups' ie with renal or hepatic impairment, in adolescence, obesity or after age 40. Specifically, and on examining the pharmacometric work on clearance in the obese (Section 4.1), it suggests it is important that pharmacovigilance is undertaken in obese women with Jaydess. Although the clinical data did not show a higher pregnancy rate in this group, it is possible from the pharmacokinetic simulation data. Further, that numbers of obese women in the clinical studies are small (i.e. 5 in the pivotal A52238 in the LCS12 arm). For use in other special groups clinical studies and/or monitoring in these groups also needs to be undertaken prior to being confident about the efficacy in these groups.

5. Pharmacodynamics

5.1. Studies providing pharmacodynamic data

The main pharmacodynamic (PD) parameters of interest are those of pregnancy rate and adverse effects. Menstrual cycles, bleeding patterns and return to fertility are other parameters measured. In both the pivotal Phase 2 (A46796) and Phase 3 (A52238) studies, parameters

from a subset of 12 women per treatment arm (LCS12 and LCS16) were used to determine a non-compartmental population pharmacokinetic model.

Table 8. Submitted pharmacodynamic studies.

PD Topic	Subtopic	Study ID
Primary Pharmacology	Effect on safety and efficacy	A46796 Multi-center, open, randomized, dose finding phase II study to investigate for a maximum of three years ultra low dose levonorgestrel contraceptive intrauterine systems (LCS) releasing *in vitro* 12 µg/24 h and 16 µg/24 h of levonorgestrel compared to MIRENA in nulliparous and parous women in need of contraception. A52238 Phase III Multi-center, open-label, randomized study to assess the safety and contraceptive efficacy of two doses (*in vitro* 12µg/24 h and 16µg/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 16µg/24 h dose group (LCS16 arm) up to 5 years
		91775 Multi-center, open label, single arm study to assess efficacy, safety, bleeding pattern and pharmacokinetics of the ultra low dose levonorgestrel intrauterine contraceptive system (LCS) for a maximum of 3 years in women 18 to 40 years of age
Secondary Pharmacology	Effect on bone mineral density	Examination of effects on bone mineral density is a substudy of A52238
	Effect on estradiol concentrations	The observed estradiol concentrations seen in A52238 are within the typical range of normal menstrual cycles.
	Effect on cervix	The three formulations investigated in the phase 2 study, A46796 showed an increase in the systemic exposure in the order LCS12 (this application) LCS16 and Mirena. There was no difference in the effect on the endometrium or on the cervix
	Effect on endometrium	Endometrial safety was also substudy of A 52238
Gender other genetic and Age-Related Differences in PD Response	Effect of gender	Used only in women
	Effect of age	Physiology-based pharmacokinetic (PBPK) modeling via the software PK-Sim® used to explore the expected pharmacokinetic properties

PD Topic	Subtopic	Study ID
		of LCS in females of different ages
PD Interactions		Nil likely to be relevant
Population PD and PK-PD analyses	Healthy subjects	Healthy subjects A57262 External validation of an IVIVC for the low dose levonorgestrel contraceptive system

None of the pharmacodynamic studies had deficiencies that excluded their results from consideration.

5.2. Summary of pharmacodynamics

The information in the following summary is derived from conventional pharmacodynamic studies in humans unless otherwise stated.

5.2.1. Mechanism of action

The dose of LNG released daily results in tissue concentrations that result in the endometrium becoming relatively insensitive to circulating estradiol. It also thickens the cervical mucus which impedes the passage of sperm through the cervical canal thereby preventing fertilization.

5.2.2. Pharmacodynamic effects

5.2.2.1. Primary pharmacodynamic effects

5.2.2.1.1. Contraceptive reliability (number of pregnancies)

Contraceptive reliability was analyzed using two different methods: the Pearl Index (PI) and a Kaplan-Meier (life table) analysis. This is in accordance with the Committee for Medicinal Products for Human Use (CHMP) 'Guideline on Clinical Investigation of Steroid Contraceptives in Women' (EMEA 2005) (1).

The primary pregnancy rate is based on data from women 18 to 35 years of age during the first year of use (Year 1 PI) and for the total treatment duration of 3 years (3-year PI) in the pivotal study A52238.

5.2.3. Secondary pharmacodynamic effects

Not described in detail in the main body of this report.

5.2.4. Time course of pharmacodynamic effects

The primary PD effect - pregnancy prevention, occurs from the first menstrual cycle until 36 months. With regard to the specific time course, using the data from study A57262, the *in vitro* release rate data and the IVIVC model were used to predict the *in vivo* release rates. These include an early period (Day 18-25) which was also used for release of the product in clinical trials, the release rate at the end of 3 years and an average release over the entire of use.

The predicted characteristic *in vivo* release rates for LCS12 and LCS16 at the beginning, the end and on average during the use of LCS12:

Table 9. Predicted characteristic *in vivo* release rates for LCS12 and LCS16

Parameter	*In vivo* release rate (µg/day)
Early release (Day 25)	10

Parameter	*In vivo* release rate (µg/day)
Average release	6.4 (3 years)
Release at the end of 3 years	4.8

5.2.5. Relationship between drug concentration and pharmacodynamic effects

As seen in the pharmacodynamic studies the 'minimum' release rate (based on the IVIC) is approximately above 5µg /day, as this was the '*in vitro*' release rate at the end of the 3 years. It should be noted that the *in vivo* release rates were estimated based on *ex vivo* residual content data obtained with Jaydess in the Phase III study. Additionally, *ex vivo* residual content data was determined in IUSs from women who prematurely discontinued or completed the study. Based on these data, an *in vitro-in vivo* correlation (IVIVC) was developed.

Although there is plenty of data relating serum drug concentrations of LNG and contraceptive effect, with an IUS the local release rates are more clinically relevant as Jaydess has low systemic serum LNG concentrations (below 121 ng/L in the submission). This compares with typical maximum concentrations of LNG after daily oral administration of a combined oral contraceptive containing 100 µg LNG and which are about 4500 ng/L. Thus, LNG serum concentrations after insertion of Jaydess are more than 35 times lower than those observed after administration of a widely used combined oral contraceptive.

Further, in the two clinical studies that in the majority of women treated with Jaydess the ovarian activity was not influenced confirming the low systemic pharmacological effect of Jaydess outside the uterus.

5.2.6. Genetic-, gender- and age-related differences in pharmacodynamic response

Genetic differences were not examined.

The IUS will be used in women only therefore male studies are not required.

Age was considered – a study of women between menarche and aged 18 is underway (14371-not reported) and the two pivotal studies cross the reproductive spectrum (18-40) and include parous and nulliparous women.

5.2.7. Pharmacodynamic interactions

Pharmacodynamic interactions were not presented but with low serum concentrations and the predominant site of action being local are not expected to be clinically relevant.

5.3. Evaluator's overall conclusions on pharmacodynamics

In summary, the pharmacodynamics parameters and the methods by which they are measured are appropriate for the indication. They include the target group, and studies to examine the lower dose of LNG as compared to the currently TGA registered LNG IUS product are appropriate. In my opinion and including the Phase 3b studies underway no further studies on specific parameters are required from a pharmacodynamics perspective. However the 5 year arm of the LCS16 group and the data from Phase 3B studies are important to corroborate the early pharmacodynamics data presented here.

6. Dosage selection for the pivotal studies

There is already a 52 mg LNG IUS available in Australia (Mirena). This IUS releases LNG over 5 years. LCS12 (Jaydess) was designed to release smaller amounts of LNG per day (12 µg/day for Jaydess) and to be removed after 3 years. As there is now many years of safety data for Mirena,

the main 2 issues for the clinical use of Jaydess is whether the clinical effectiveness is maintained (in terms of pregnancy prevention) over the 3 years with a much lower LNG release, and whether there are any safety concerns with the formulation or structure of the IUS. The 2 clinical studies (A52238 and A46796) investigate these issues with LCS 12 (Jaydess). The study population characteristics summarized below are the same for the efficacy and safety analysis because the full analysis set (FAS) is identical for the efficacy and safety assessment.

7. Clinical efficacy

Proof of the clinical efficacy of LCS12 is based on the number of pregnancies in the two clinical studies (A52238 and A46796).

7.1. Contraception for up to 3 years in nulliparous and parous women

7.1.1. Pivotal efficacy studies

There was one pivotal study (A52238) and a supporting Phase II study (A46796). Both studies will be discussed together as much of the study design was similar. When it was not this will be highlighted. Further, there was a pooled analysis which combined data from both studies and which will be referred to in summary statistics.

7.1.1.1. Study A52238 and A46796

7.1.1.1.1. Study design, objectives, locations and dates

The study population characteristics summarized below are the same for the efficacy and safety analysis because the full analysis set (FAS) is identical for the efficacy and safety assessment. The FAS was defined as including all women for whom the IUS was inserted (in A46796) or the insertion of an IUS was attempted (in A52238), according to the treatment actually received.

- **Study A52238 (310442)**

This was a Phase III study undertaken in Europe, US, Canada, South America. It was a multicentre, randomised, open-label, 2-arm (LCS12 and LCS16), parallel group 3 years (up to 5 years for LCS16 only) and recruited generally healthy, 18- to 35-year old nulliparous or parous women in need of contraception. There were 1432 women in the LCS12 and 1452 in the LCS16 group. The primary efficacy variable was pregnancy rate (PI). A secondary analysis was performed using the Kaplan-Meier (life table) method. Secondary efficacy variables included assessments of bleeding patterns as recorded in subject-kept diaries. Safety variables were adverse events (AEs), laboratory variables, physical and gynaecological examinations, and vital signs. Other variables measured included dysmenorrhoea (via diaries), LCS insertion/removal ease and pain, compliance, user satisfaction (via questionnaires), ovarian and cervical function (Insler score), endometrial histology, pharmacokinetic parameters, bone mineral density (all in subset populations), discontinuations due to problems related to menstrual bleeding or amenorrhea, expulsion rate, the number of overall discontinuations, and data concerning return-to-fertility.

- **Study A46796 (308901)**

The phase 2 study A46796 was a multicentre, open-label, randomised, dose finding study to investigate LCS12 and LCS16 compared to Mirena for a maximum of 3 years. The study was performed in five European countries (Finland, Hungary, Norway, Sweden, and the United Kingdom). Parous or nulliparous women of 21 to 40 years of age (inclusive) with good general health and in need of contraception were to be included. There were 240 women in the LCS12, 245 in the LCS 16 group and 256 in the Mirena group. The number of pregnancies was recorded and the pregnancy rate (PI) was calculated as the primary efficacy variable. A secondary analysis was performed using the Kaplan-Meier (life table) method. Bleeding patterns were

evaluated from bleeding data obtained from subject-kept diaries as secondary efficacy variables. Safety measurements were assessments of AEs, laboratory variables, physical and gynaecological examinations, and vital signs. Other secondary variables measured in subsets of women were ovarian and cervical function, and endometrial histology. Further evaluations included ease and pain assessment on IUS insertion/removal, IUS expulsion rate, discontinuation rate, compliance, return-to-fertility, and pharmacokinetic parameters.

7.1.1.1.2. Inclusion and exclusion criteria

Inclusion and exclusion criteria were mostly identical between the pivotal study A52238 and supporting study A46796. Nulliparous and parous women of reproductive age and in good general health, seeking contraception with no contraindications for IUS use were screened for participation in these studies. The only potentially relevant differences between the two studies is a small difference in different inclusion criteria regarding age, i.e. 18 to 35 years in study A52238 compared to 21 to 40 years in study A46796 (mean age: 27 versus 32 years). The following Table below sums up the major differences between the resulting demographic profile included in the 2 studies.

Table 10. Summary of major differences between the resulting demographic profile included in studies A52238 and A46796.

Parameter	A52238	A46796
Age (median, years)	27	32
Ethnicity	Predominantly Caucasian	Predominantly Caucasian
BMI	25.32 kg/m^2	24.05 kg/m^2
BMI> 30 kg/m^2	17%	7.5%
Nulliparous	38.8%	21.7%

7.1.1.1.3. Study treatments

In the pivotal study A52238, a total of 2884 women with an insertion attempt were assigned to the FAS of the study, with 1432 women on LCS12 and 1452 women on LCS16. The mean treatment duration for the LCS12 group was 821 days or 2.25 women years (wy) and 843 days or 2.31 wy for the LCS16 group.

In study A46796, a total of 741 women were included in the FAS: 240 women in the LCS12 group, 245 women in the LCS16 group and 256 women in the Mirena group. The mean treatment duration was 915 days or 2.51 wy in the LCS12 group, 912 days or 2.50 wy in the LCS16 group, and 895 days or 2.45 wy in the Mirena group.

For the pooled analysis, cumulative treatment exposure for women on LCS12 was 1488 wy for the first year, and 3779 wy at three years of treatment. The cumulative exposure for LCS16 was very similar to that for LCS12. The exposure was shorter in the Mirena arm (first year: 236 wy; three years: 619 wy) due to the smaller number in the Mirena group. The pooled analysis showed a trend toward shorter mean exposure time in younger and nulliparous women. On average, the mean exposure for women on LCS12 in the youngest age group or nulliparous group was approximately 60 or 40 days shorter when compared to the overall population.

The overall profiles of medical history, prior or concomitant medication were comparable across the studies and between the treatment groups. The most frequently used concomitant medications recorded over a treatment period of three years were ibuprofen and paracetamol including medication for pain, or prophylaxis of pain associated with the insertion procedure or

used for a wide variety of reasons at any time during the 3 year treatment period; others less frequently used were antibiotics and antifungals.

7.1.1.1.4. Efficacy variables and outcomes

The primary efficacy outcome was contraceptive reliability; assessed by calculating the PI and performing a life-table analysis.

- Pearl Index (PI) - The PI for the 3 years of treatment (i.e. 3-year PI) and for the first year of treatment (i.e. Year 1 PI) were the primary criteria to assess the contraceptive reliability of LCS12. As the PI usually assumed to be constant over time, and as this cannot automatically be assumed for the study treatments, several different prespecified PIs were also calculated.
  - 'First year PI' was the PI obtained in the first year of treatment, i.e., number of pregnancies that occurred during the first year of treatment divided by time (in 100 women years). Primary outcome
  - 'Second year PI', PI obtained in the second year of treatment, i.e., number of pregnancies that occurred during the second year of treatment divided by time (in 100 women years)
  - 'Third year PI', PI obtained in the third year of treatment, i.e., number of pregnancies that occurred during the third year of treatment divided by time (in 100 women years)
  - 'Two years PI', PI obtained in the first two years of treatment, i.e., number of pregnancies that occurred during the first two years of treatment divided by time (in 100 women years) the women were under risk of getting pregnant in the first two years of treatment.
  - 'Three years PI', PI obtained in the first three years of treatment, i.e., number of pregnancies that occurred during the first three years of treatment divided by time (in 100 women years). Primary outcome
  - 'Overall PI', PI obtained during the whole study, i.e., number of pregnancies that occurred during treatment divided by the time the women (in 100 women years)
    - Unadjusted and adjusted PIs were calculated
- Life Table analysis using a Kaplan-Meier analysis on the basis of pregnancies occurring during study treatment.

A negative pregnancy result was a prerequisite for the IUS insertion. Pregnancy tests were also performed at the final study visit. In study A46796, home pregnancy tests were also performed on monthly basis.

Other efficacy outcomes included:

- *Menstrual bleeding analysis* - Based on the day-to-day information obtained from the diary cards, menstrual bleeding patterns were reported using descriptive statistics. The bleeding pattern indices include number of days of bleeding and/or spotting, and analysis of the episodes of bleeding and spotting, bleeding only and spotting only. Menstrual bleeding patterns were analysed by reference periods: 90-day reference periods over the 3-year treatment, and 30-day reference periods for the first year of treatment. For each 90-day reference period, the proportion of women with amenorrhea, prolonged, frequent, infrequent and irregular bleeding was calculated.
- *Treatment compliance* - Study drug compliance (i.e. IUS location) was verified by ultrasound at all visits after insertion. The woman was considered compliant with the study treatment if the IUS was located in the fundal position or was displaced but still completely within the uterine cavity. In addition, the presence of the removal threads was checked at each visit.

- If the IUS was partially or totally expelled or if it had perforated the cervix or the body of the uterus during the treatment period the woman was withdrawn from the study. Expulsions were counted but only some were reported as an AE.
- *Return to fertility*- the time to return-to-fertility was followed for up to a year in all women who discontinued treatment because of wish for pregnancy. Women were instructed to contact the study site if they became pregnant within 3 months after their end of study visit (all women in both studies). In study A52238 all women were contacted by the sites 3 months after the end of study treatment. Women who had discontinued the study because of a wish for pregnancy were to be contacted by the study site 12 months after the end study treatment (ongoing at the time of the submission). All women in study A46796 were to be contacted by the study site at 3 and 12 months after the end study treatment to gather information on after treatment pregnancies.
- *User satisfaction questionnaire* - User satisfaction was evaluated only in the pivotal study A52238 (after implementation of protocol amendment 3). Women were asked to fill in user satisfaction questionnaires at the end-of-study visit. The degree of user satisfaction was assessed in eight questions.

7.1.1.1.5. Randomisation and blinding methods

For study A46796, randomisation was undertaken using a computer generated code (global biostatistics). For study A52238, randomisation was undertaken using a computer generated code (global biostatistics).

A46796. Although in the study report it states that "the study was not blinded" (page 34 of study report), as the subjects were not aware of which IUS they had the study is technically single blind.

A52238. The study was open, however all evaluators of efficacy and safety apart from the investigators and study nurses were to be blinded. The allocated treatment was not be revealed to the patient prior to the completion of the study.

For the supportive 10982 (A Multicenter, Open-Label, Non-Randomized Study of SH G 00650 (Mirena) A Levonorgestrel Intrauterine System) in Parous Women Seeking Contraception to Evaluate its Efficacy, Safety, and Pharmacokinetic Profile When Inserted for 12 months) there was no randomisation, however this was a study of a higher dose and longer insertion time of LNG. This was not re-evaluated.

7.1.1.1.6. Analysis populations

The full analysis set (FAS) was defined as including all women for whom the IUS was inserted or the insertion of an IUS was attempted, according to the treatment actually received. The FAS is identical for the efficacy and safety assessment.

7.1.1.1.7. Sample size

- **A46796**

This was a dose-controlled, 3-arm, parallel group, phase II dose-finding study. Two doses of IUS administered LNG: 12 and 16 µg per day and compared to MIRENA (20 µg LNG per day). The sample size was designed to rule out an 'unacceptable' pregnancy rate in the study arm and to rule out treatment failure, as to show non-inferiority against MIRENA, using as an endpoint a PI initially set at 0.2 per 100 woman years, 1000 women would have been needed in the LCS12 arm. In summary, a total of 690 generally healthy 21 to 40-year old fertile women in need of contraception were thus planned to be randomised to 3 equal-sized treatment arms of 230 women each. Actually 742 women were randomised and a total of 738 women were included in the FAS: 239 women in the LCS12 group, 245 women in the LCS16 group and 254 women in the Mirena group.

Exposure: The mean treatment duration was 915 days or 2.51 wy in the LCS12 group, 912 days or 2.50 wy in the LCS16 group, and 895 days or 2.45 wy in the Mirena group. For the pooled population across the two studies, the cumulative treatment exposure for women on LCS12 was 1488 wy for the first year, and 3779 wy at three years of treatment. The cumulative exposure for LCS16 was very similar to that for LCS12, but it was shorter in the Mirena group (first year: 236 wy; three years: 619 wy).. Based on the pooled analysis, a trend toward shorter mean exposure time was seen for younger and nulliparous women. On average, the mean exposure for women on LCS12 in the youngest age group or nulliparous group was approximately 60 or 40 days shorter when compared to the overall population.

The following subsets of the study population were defined for the analysis

- Subset 1: Ovarian and cervical function (studied in 60 subjects, 20 per treatment arm)
- Subset 2: Endometrial histology (studied in 90 subjects, 30 per treatment arm)
- Subset 3: Pharmacokinetics (studied in 36 subjects, 12 per treatment arm) – already discussed in Section 4.1

Time points for data collection are screening, baseline, months 1, 6, 12, 18, 24, 30 and 36 (end-of-study visit).

All tabulations, listings, graphs and analyses were undertaken using SAS in the currently available production environment at Bayer Schering Pharma.

- **A52238**

This was a multi-center, randomized, open-label, 2-arm, parallel-group phase 3 study. Two doses of levonorgestrel 12 µg and 16 µg per day, administered via an IUD were studied. There was no control group. The LCS 12 µg was continued for up to 3 years and the 16 µg treatment arm was continued for up to 5 years.

It was planned that a total of 2820 generally healthy women 18 to 35 years of age desiring contraception would be randomised to 2 equal-sized treatment arms (1410 subjects per dose). In fact, a total of 2884 women with an insertion attempt were included in the FAS, with 1432 women on LCS12 and 1452 women on LCS16.

It was planned a priori that additional variables would be studied in 4 subsets in pre-selected centers. These subsets were:

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

It should be noted that the Full analysis set (FAS) includes all subjects randomised who received treatment (had at least one insertion attempt, even if unsuccessful), using the treatment actually received. All safety and efficacy evaluations were conducted on the FAS.

Exposure: The mean treatment duration for the LCS12 group was 821 days or 2.25 women years (wy) and 843 days or 2.31 wy for the LCS16 group.

7.1.1.1.8. Statistical methods

There were 3 datasets

1. FAS – For A46796; this analysis set included all randomised subjects who had a successful insertion and it was analysed according to the treatment actually received. For A52238 and

the pooled analysis, all randomised women with a successful or non successful insertion were included in the FAS, which was the set used for all safety and efficacy analyses.

2. Per Protocol set (PPS)

For A46796, the PPS (in the study protocol called 'valid case analysis set') applied to the primary efficacy variable (i.e. the PI). A subject was excluded from the PPS for the following reasons:

- use of another experimental drug
- other major protocol deviation present

However in the analyses, the FAS and the PPS were identical.

There was no PPS in the A52238.

3. Safety analysis set (SafetyAS)

No safety dataset was defined as FAS was used for safety analysis.

7.1.1.1.9. Participant flow

- **Study A46796**

742 randomised to LCS12 (240), LCS16 (246) and Mirena (256) respectively. In the first year, 1 in LCS12 failed insertion (cervical abnormality), 1 LCS16 failed insertion (technical) and 2 Mirena failed insertion (1 vasovagal, 1 cervical).

This gave LCS12 239, LCS16 245 and Mirena 254 women who were treated. These were the women included in the FAS, PPS and SAS.

Of the 239, 245 and 254 women treated in the three groups, there were 24, 33 and 36 premature discontinuations respectively, primarily for AEs.

This gave 215, 212 and 218 women entering Year 2 respectively.

Then 28, 23 and 25 premature discontinuations respectively in Year 2, primarily for AEs.

This gave 187,189, 193 women entering into Year 3 respectively.

Then 13, 15, 11 premature discontinuations respectively in Year 3, primarily AEs and loss to followup.

Overall 174,174,182 women completed the study in the three respective arms.

Table 11. Number of premature discontinuations after randomisation, with reasons

	LCS12 N=239 (%)	LCS16 N=245 (%)	Mirena N= 254 (%)	Total = 738 (100%)
Completed	174 (72.8)	174 (71)	182 (71.7)	530 (71.8)
Prematurely discontinued	65 (27.2)	71 (29)	72 (28.3)	208 (28.2)
Reason for discontinuation				
Withdrawal of consent	1 (1.5)	2 (2.8)	0 (0)	2 (1.4)
Protocol	2 (3.1)	2(2.8)	1 (1.4)	5 (2.4)

	LCS12 N=239 (%)	LCS16 N=245 (%)	Mirena N= 254 (%)	Total = 738 (100%)
deviation				
Adverse event	41 (63.1)	43 (60.6)	48 (66.7)	132 (63.5)
Lost to follow up	0	4(5.6)	0	5 (2.4)

- **Study A52238**

A total of 3661 women were screened for inclusion in the study, with 2885 randomised. One subject was randomized but no insertion was attempted and was excluded from the FAS of 2884 subjects. Of the 776 women (21.2%) who were screened but not randomised, 401 did not meet the inclusion and exclusion criteria, 164 withdrew consent, 85 had no further information available, 44 could not be included due to pregnancy, and 82 discontinued for other reasons which were not easy to find in the submission. The women in the study were recruited from 138 centers in 11 countries.

During the first year of treatment, 511 subjects (17.7%) prematurely discontinued the study treatment and in the second year of treatment 397 subjects (16.7%) prematurely discontinued treatment. During the third year of treatment, 285 subjects discontinued 14.4%) and these were fairly evenly distributed between the treatment group. The reason for most premature discontinuations in both treatment groups was an adverse event, with a slightly higher proportion occurring in the LCS12 group. The reason for discontinuation labelled "other" included a large number of women who discontinued due to a wish for pregnancy (LCS12: 115, LCS16: 117), and smaller numbers who had no further need for contraception, who could not attend visits, who had a failed insertion (13 subjects), or who had other personal reasons.

Table 12. Number of premature discontinuations after randomisation

	LCS12 no. (%)	LCS16 no. (%)	Total no. (%)
	1432 (100)	1453 (100)	2885 (100)
Study medication never administered	0.2 (0.1)	2 (<0.1)	
Completed first 3 years	819 (57.2)	870 (59.9)	1689 (58.5)
Prematurely discontinued	612 (42.7)	581 (40.0)	1193 (41.4)
Missing	1 (<0.1%)	0 1 (<0.1%)	
Reason for discontinuation	613 (100)	583 (100)	1196 (100)
Withdrawal of consent	26 (4.2)	31 (5.3)	57 (4.8)
Protocol deviation	16 (2.6)	16 (2.7)	32 (2.7)

	LCS12 no. (%)	LCS16 no. (%)	Total no. (%)
Adverse event	313 (51.1)	278 (47.7)	591 (49.4)
Lost to follow-up	63 (10.3)	61 (10.5))	124 (10.4)
Pregnancy	9 (1.5)	10 (1.7)	19 (1.6)
Other	186 (30.3)	186 (31.9)	372 (31.1)

Slightly fewer women with one or more births discontinued due to withdrawal of consent or an AE than nulliparous women (20.7% vs. 25.2%). In general the number of women dropping out due to bleeding or investigator-assessed, progestin-related side effects was low in both parous and nulliparous women and in both treatment groups.

7.1.1.1.10. Major protocol violations/deviations

Exposure times were subtracted if alternative contraception used.

In A46796, at each visit, the subject reported whether concomitant use of other contraceptive methods took place or not after the previous visit. If so, the period of concomitant contraceptive method use was excluded from the exposure time calculated for that subject. Occasional use was therefore able to be adjusted for, but the time period between the preceding visit and the current visit was excluded if the subject was using often.

In A52238, use of subject diaries enabled the time of any use of other contraception to be removed from the PI exposure time calculation.

7.1.1.1.11. Baseline data

- **Study A46796**

[Baseline data is described in an Appendix not included in this Extract.]

- **Study A52238**

[Baseline data is described in an Appendix not included in this Extract.]

7.1.1.1.12. Results for the primary efficacy outcome

PEARL INDEX (PI)

Unadjusted and adjusted PIs were calculated; the differences between the unadjusted and adjusted PIs were in the calculation of the crude exposure time in case of IUS expulsion (total or partial). Furthermore, pregnancies that occurred after the IUS was known not to be *in situ* or displaced in the uterus were not to be counted for the adjusted PI. The resulting differences in the relevant exposure times were very small; thus, the unadjusted and adjusted PIs are very similar if not identical.

- **Study A52238**

In this study, a total of 20 pregnancies were observed under treatment; 10 in each treatment group. Of these, 3 in the LCS12 group (30%) and 7 in the LCS16 group (70%) were ectopic. Of the remaining 7 pregnancies in the LCS12 group, 3 pregnancies ended in spontaneous abortion and 1 in induced abortion, 2 pregnancies were normal and carried to term, and 1 pregnancy was delivered prematurely by cesarean section due to preeclampsia, with a normal fetal outcome. Of the 3 remaining pregnancies in the LCS16 group, 1 was a blighted ovum that ended in spontaneous abortion, 1 was a spontaneous abortion, and 1 pregnancy was normal and carried to term.

Examining the yearly PIs for all women in the pivotal study A52238 it can be seen that for 18- to 35-year old women, the unadjusted PI for LCS12 for the first year was 0.41 with the upper limit of the two-sided 95% CI of 0.96, and PI=0.33 for the total three years of use, with the upper limit of the two-sided 95% CI of 0.60. The CHMP recommend that the difference between the point estimate and the 95% CI of the PI is <1.

Table 13. PIs by year of treatment for women 18 to 35 years of age, 3-year and Year 1 PIs by subgroup and treatment, unadjusted – FAS, study A52238

LCS12					LCS16			
Year	**No. women / no. preg-nancies**	**Relevant exposure time (wy)**	**Pearl index unadj-usted**	**Upper 95% CI**	**No. women / no. preg-nancies**	**Relevant exposure time (wy)**	**Pearl index unadj - usted**	**Upper 95% CI**
PI by year of treatment and over 3 years, women 18 to 35 years of age (all women in study)								
Y 1 PI	1432 / 5	1217.78	0.41	0.96	1452 / 2	1252.78	0.16	0.58
Y 2 PI	1162 / 3	1015.67	0.30	0.86	1206 / 4	1067.49	0.37	0.96
Y 3 PI	960 / 2	825.17	0.24	0.88	1010 / 4	891.09	0.45	1.15
3-year PI	1432 / 10	3058.62	0.33	0.60	1452 / 10	3211.36	0.31	0.57
3-year PI, women 18 to 35 years of age and by subgroup								
Age								
18-35	1432 / 10	3058.62	0.33	0.60	1452 / 10	3211.36	0.31	0.57
18-25	566 / 4	1114.21	0.36	0.92	564 / 2	1207.19	0.17	0.60
26-35	866 / 6	1944.41	0.31	0.67	888 / 8	2004.17	0.40	0.79
Parity								
Nulli-parous	556 / 4	1110.63	0.36	0.92	574 / 3	1205.33	0.25	0.73
Parous	876 / 6	1947.99	0.31	0.67	878 / 7	2006.03	0.35	0.72
BMI								
<30 kg/m	1187 / 9	2547.32	0.35	0.67	1198 / 6	2664.82	0.23	0.49

LCS12					LCS16			
Year	No. women / no. preg-nancies	Relevant exposure time (wy)	Pearl index unadj-usted	Upper 95% CI	No. women / no. preg-nancies	Relevant exposure time (wy)	Pearl index unadj - usted	Upper 95% CI
^{2}								
≥30 kg/m^2	244 / 1	509.34	0.20	1.09	250 / 4	538.41	0.74	1.90

The unadjusted 3-year PIs for all women, 18 to 35 years of age were similar in LCS12 and 16. The unadjusted 3-year PI for younger women (18 to 25 years) was greater in the LCS12 than the LCS16 group but not in the older group (26 to 35 years).

The unadjusted 3-year PIs were similar for parous and nulliparous women within and across the treatments but numerically higher for LCS 12. The CIs of the two BMI categories overlap suggesting (although this is a post hoc analysis) that PI is unlikely to be affected by the BMI.

There were no relevant differences in the Year 1 PI between the nulliparous and parous women treated with LCS12. In terms of effect of body size on PI, the small size of the subgroup of women with BMI ≥ 30 kg/m^2 does not allow for a detection of differences here. However, the widely overlapping 95% CIs between the subgroups suggests no differences in the PI based on the BMI.

There are no relevant differences in the PIs between the pivotal study A52238 and the pooled analysis. For the LCS12 treatment, the pooled data is driven by data in A52238 which had most of the pregnancies (10 versus 1), and PIs based on the pooled data are almost the same as in A52238.

- **Study A46796**

In study A46796, 6 pregnancies were observed during treatment: 1 (an ectopic pregnancy) in the LCS12 group and 5 in the LCS16 group (2 ectopic, 2 ended in spontaneous abortion and one the result of an unnoticed expulsion - this pregnancy was normal and carried to term). There were no pregnancies in the Mirena group.

Table 14. Unadjusted Pearl Index A46796

Treatment	Time	Total exposure [WY]	Relevant exposure [WY]	Number of pregnancies	Pearl index	Lower 95% CIL	Upper 95% CIL
LCS12	Overall	601.68	597.17	1	0.17	0.00	0.93
LCS16	Overall	611.48	606.66	5	0.82	0.27	1.92
LCS12&16	Overall	1213.16	1203.83	6	0.50	0.18	1.08
Mirena	Overall	627.94	621.98	0	0.00	0.00	0.59
LCS12	Year 1	226.07	225.13	0	0.00	0.00	1.64
LCS16	Year 1	233.30	232.84	1	0.43	0.01	2.39
LCS12&16	Year 1	459.36	457.97	1	0.22	0.01	1.22
Mirena	Year 1	239.35	237.71	0	0.00	0.00	1.55
LCS12	Year 2	196.48	195.77	1	0.51	0.01	2.85
LCS16	Year 2	197.93	196.97	3	1.52	0.31	4.45
LCS12&16	Year 2	394.41	392.74	4	1.02	0.28	2.61
Mirena	Year 2	201.06	199.96	0	0.00	0.00	1.84
LCS12	Year 3	176.25	174.17	0	0.00	0.00	2.12
LCS16	Year 3	177.25	174.72	1	0.57	0.01	3.19
LCS12&16	Year 3	353.50	348.89	1	0.29	0.01	1.60
Mirena	Year 3	184.75	182.04	0	0.00	0.00	2.03
LCS12	2 years	422.55	420.90	1	0.24	0.01	1.32
LCS16	2 years	431.22	429.81	4	0.93	0.25	2.38
LCS12&16	2 years	853.77	850.71	5	0.59	0.19	1.37
Mirena	2 years	440.41	437.67	0	0.00	0.00	0.84
LCS12	3 years	598.79	595.07	1	0.17	0.00	0.94
LCS16	3 years	608.47	604.53	5	0.83	0.27	1.93
LCS12&16	3 years	1207.27	1199.60	6	0.50	0.18	1.09
Mirena	3 years	625.16	619.71	0	0.00	0.00	0.60

The adjusted and unadjusted 3-year Pearl indices (PI) were identical (LCS12: 0.17, LCS16: 0.83, Mirena: 0) because no pregnancy was excluded for the calculation of the adjusted PIs. The upper limits of the 95% confidence interval (CI) were below 2 for all 3 treatment groups. Since no pregnancies occurred in the Mirena group, the PI for this group was 0 at all time points.

The highest PI (unadjusted PI: 1.52; adjusted PI: 1.53) was observed in Year 2 for the LCS16 arm. With the exception of this group and time, all PI were below 1 and the upper limit of the 95% CI never exceeded 4.5.

Note: the requirement of the EMEA guidance, that the difference between the point estimate for the Pearl index and the upper 95% CI limit should not exceed 1, is met for the three year Pearl index of Mirena and LCS12, even though this was only a phase 2 study. The requirement was thus missed for LCS16.

As the risk of ectopic pregnancy has been a concern with previous IUDs, this aspect of the submission is of interest. Specifically, the risk of ectopic pregnancy was 0.2% for LCS12 and 0.5% for LCS16 in the A55238 study, and 0.4% for LCS12, 0.8% for LCS16 and 0% for Mirena in the A46976 study (See Section 8.3).

LIFE TABLE ANALYSIS (Kaplan-Meier analysis)

- **Study A52238**

A life table analysis was performed to obtain data on cumulative failure rate (i.e. probability of becoming pregnant) over the 3 years of treatment by age, parity and BMI groups, by year of treatment for all women in the pivotal study A52238.

Table 15. Cumulative, 3-year failure rate by subgroup and treatment and by year of treatment for women 18 to 35 years of age, unadjusted – FAS, study A52238

	N	No. pregnancies	Relevant exposure time (wy)	Cum. failure rate	Lower 95% CL	Upper 95% CL
LCS12						
Year 1	1432	5	1217.78	0.004	0.002	0.010
Year 2	1162	3	1015.67	0.003	0.001	0.009
Year 3	960	2	825.17	0.002	0.001	0.009
Cumulative, 3-year failure rate for women 18 to 35 years of age and by subgroup						
Age						
18-35 years	1432	10	3058.62	0.009	0.005	0.017
18-25 years	566	4	1114.21	0.010	0.004	0.027
26-35 years	866	6	1944.41	0.008	0.004	0.019
Parity						
Nulliparous	556	4	1110.63	0.010	0.004	0.026
Parous	876	6	1947.99	0.009	0.004	0.019
BMI						
<30 kg/m^2	1187	9	2547.32	0.010	0.005	0.019
≥30 kg/m^2	244	1	509.34	0.005	0.001	0.033
LCS16						
Year 1	1452	2	1252.78	0.002	0.000	0.007
Year 2	1206	4	1067.49	0.004	0.001	0.010
Year 3	1010	4	891.09	0.004	0.002	0.011
Cumulative, 3-year failure rate for women 18 to 35 years of age and by subgroup						

	N	No. pregnancies	Relevant exposure time (wy)	Cum. failure rate	Lower 95% CL	Upper 95% CL
Age						
18-35 years	1452	10	3211.36	0.010	0.005	0.018
18-25 years	564	2	1207.19	0.005	0.001	0.020
26-35 years	888	8	2004.17	0.012	0.006	0.025
Parity						
Nulliparous	574	3	1205.33	0.008	0.005	0.026
Parous	878	7	2006.03	0.010	0.005	0.022
BMI						
<30 kg/m^2	1198	6	2664.82	0.007	0.003	0.016
≥30 kg/m^2	250	4	538.41	0.022	0.008	0.057

For 18- to 35-year old women, the cumulative failure rate (Kaplan-Meier estimate) at year 1 was 0.4% and 0.9% for three years.

There were no relevant differences in the unadjusted, cumulative 3-year failure rate for women 18 to 35 years of age. Subgroup analyses did not show any relevant differences between the subgroups within the LCS12 treatment.

- **Study A46796**

Probability of getting pregnant, using Kaplan-Meier Life Table Analysis

The cumulative failure rate (i.e. the probability of getting pregnant, calculated using the Kaplan-Meier method as required by the EMEA guideline) led to results similar to the PI above. The cumulative failure rate over 3 years was 0.005 in the LCS12 group, 0.025 in the LCS16 group, and 0.000 in the Mirena group. The results are summarized by year below (unadjusted). The adjusted calculations were similar.

Table 16. Cumulative failure rate over 3 years summarized by year (unadjusted).

Treatment	Time	Total exposure [WY]	Relevant exposure [WY]	Number of pregnancies	Cumulative probability of getting pregnant	Lower 95% CIL	Upper 95% CIL
LCS12	Year 1	226.07	225.13	0	0.000	.	.
LCS16	Year 1	233.30	232.84	1	0.004	0.001	0.030
LCS12&16	Year 1	459.36	457.97	1	0.002	0.000	0.015
Mirena	Year 1	239.35	237.71	0	0.000	.	.
LCS12	Year 2	196.48	195.77	1	0.005	0.001	0.036
LCS16	Year 2	197.93	196.97	3	0.015	0.005	0.047
LCS12&16	Year 2	394.41	392.74	4	0.010	0.004	0.027
Mirena	Year 2	201.06	199.96	0	0.000	.	.
LCS12	Year 3	176.25	174.17	0	0.000	.	.
LCS16	Year 3	177.25	174.72	1	0.006	0.001	0.042
LCS12&16	Year 3	353.50	348.89	1	0.003	0.000	0.021
Mirena	Year 3	184.75	182.04	0	0.000	.	.
LCS12	2 years	422.55	420.90	1	0.005	0.001	0.037
LCS16	2 years	431.22	429.81	4	0.019	0.007	0.051
LCS12&16	2 years	853.77	850.71	5	0.012	0.005	0.030
Mirena	2 years	440.41	437.67	0	0.000	.	.
LCS12	3 years	598.79	595.07	1	0.005	0.001	0.036
LCS16	3 years	608.47	604.53	5	0.025	0.011	0.060
LCS12&16	3 years	1207.27	1199.60	6	0.015	0.007	0.034
Mirena	3 years	625.16	619.71	0	0.000	.	.

7.1.1.1.13. Results for other efficacy outcomes

- **MENSTRUAL BLEEDING**

This was analysed using the FAS.

Information on menstrual bleeding data was collected using subject-kept diaries. For the analyses, 90-day reference periods were used over the entire treatment period as per WHO recommendations. The 30-day reference periods were also used in the first year of treatment to provide a more detailed view over the time period with most rapid changes.

The evaluation of menstrual bleeding based on the pooled data across the pivotal study A52238 and study A46796 is considered representative. Results from the Mirena group from study A46796 are included in the pooled analysis although the sample size is small compared to the sample sizes in the LCS arms.

There was a clear, dose-dependent trend for an increase in the proportion of women with amenorrhea and infrequent bleeding over the course of the study and the proportion of women with prolonged and frequent bleeding decreased during the treatment period, from about 60% during the first 90-day period to about 20% during the second 90-day period. The likelihood of amenorrhea being LCS12: 11.6%, LCS16: 20.3%, Mirena: 23.3%) Infrequent bleeding was already twice as common during the second 90-day period compared to the first 90-day period of treatment.

The proportion of women with irregular bleeding decreased from around 42% or 28% during reference periods 1 and 2, respectively, and stayed fairly constant (around 16% to 19%) in the pooled LCS12 group from reference period 5 onwards, but continued to decrease in the Mirena group (reference period 11: 9.3%). In the LCS12 group, the percentage of women with irregular bleeding in reference period 11 was 16.7% (LCS16: 12.0%).

- **TREATMENT COMPLIANCE**

Compliance with the IUS treatment was evaluated at every visit by use of vaginal ultrasound. Compliance was counted if the IUS was located in the fundal position or was displaced but still

completely within the uterine cavity. The proportion of compliant women at the end of the study visit was 93% for A532238 - this could be explained by the way patients who had had their IUS removed or expelled were counted in the final visit as there was 99% compliance throughout the study. In study A46796, overall compliance was consistently over 96% in all treatment groups throughout the study with no difference between subgroups.

- **RETURN-TO-FERTILITY**

In Study A52238, women were asked to contact the site if they became pregnant within 3 months of discontinuation. All women were routinely contacted at 3 months after discontinuation. Those who had discontinued due to a wish for pregnancy were followed up again at 12 months. Collection of the 3-month and 12-month follow-up information was still ongoing at the time of submission.

In study A46796, of women with follow-up information up to 12 months, data were available for a total of 29 women who had discontinued the study drug for wish of pregnancy (LCS12: 7, LCS16: 11, and Mirena: 11 women), of whom 25 of the 29 had conceived during the 12-month follow-up (LCS12: 6, LCS16: 8, and Mirena: 11).

- **SUBJECTIVE ASSESSMENT OF USER SATISFACTION**

User satisfaction was evaluated only in the pivotal study A52238 after implementation of protocol amendment 3. Satisfaction data for women who withdrew from the study prior to Amendment 3 was therefore not collected.

Data for 1053 women in the LCS12 group and 1063 women in the LCS16 group (2116 out of 2885 women in the FAS) are available. Overall, 77.4% of were 'very satisfied' with the study treatment.

- **PHARMACOKINETICS of SILVER ION**

The Subset 3 analysis included a PK study of the silver ion. Serum concentrations were measured as planned a priori in 13 subjects from subset 3 before insertion, then at Visits 2, 6 and 10. In almost all subjects, the baseline concentration of silver in serum was below the LLOQ of 1 µg/L. In one subject in the LCS16 group, the pre-treatment concentration of silver was 1.55 µg/L. After insertion of LCS12 or LCS16, the silver ion concentration in serum was always below the LLOQ of 1 µg/L. Thus, the percentage change of serum silver ion concentrations between pre-treatment and treatment visits was not calculated.

Non clinical/biocompatibility studies have been undertaken with the silver ring. These are summarised in the dossier Module 2. The components of LCS12, which include the silver ring, are biocompatible under the conditions of the tests employed and were not mutagenic or cytotoxic.

7.2. Analysis performed across trials

A pooled analysis was undertaken and relevant data from this has been discussed as comparison in the discussion of clinical efficacy and safety endpoints when relevant.

7.3. Evaluator's conclusions on clinical efficacy

- **Pregnancy**

Although for obvious reasons, a placebo group was not studied, contraceptive efficacy of LCS12 (Jaydess) when inserted according to the insertion instructions has been met. In the pivotal study A52238 for 18- to 35-year old women, the unadjusted PI for LCS12 for the first year was 0.41 with the upper limit of the two-sided 95% CI of 0.96, and 0.33 for the total three years of

use, with the upper limit of the two-sided 95% CI of 0.60. The CHMP recommend that the difference between the point estimate and the upper limit of the 95% CI of the PI is <1.

Further, in the supporting study A46976, the highest PI (unadjusted PI: 1.52; adjusted PI: 1.53) was observed in Year 2 for the LCS16 arm. With the exception of this group and time, all PI were below 1 and the upper limit of the 95% CI never exceeded 4.5.

Note: the requirement of the EMEA guidance, that the difference between the point estimate for the Pearl index and the upper 95% CI limit should not exceed 1, which although being met for the three year Pearl index with Mirena and LCS12, was missed for LCS16.

Using a life table analysis, and using the pivotal A52238 study LCS12 has a failure rate of approximately 0.4% at 1 year and a cumulative failure rate of approximately 0.9% at 3 years.

In terms of the 95% CI of the PI for the supporting study A46796 not being met in the LCS16 arm, it is noted that this is a Phase 2 study only, that it occurred in the LCS16 and not the LCS12 (Jaydess) arm and that the failure rate also includes pregnancies due to undetected expulsions.

Demographic and baseline characteristics of the pivotal study A53328 and study A46796 revealed demographic and baseline characteristics representative of the target population with a large group of both ≤ 25 years and/or nulliparous women (approximately 600 women in each of these categories in the total LCS12 population). Further follow-up on those who wished to conceive but hadn't at the completion of the study, and vigilance in special groups is required and has subsequently been provided by the Sponsor in the S31 request.

- **Bleeding**

Jaydess had a favourable effect on bleeding as is seen with higher high dose LNG preparations. Specifically, the proportion of women with amenorrhea gradually increased over the course of the 3year treatment period although the number was relatively small compared to the effect with Mirena. Additionally, the proportion of women with prolonged and frequent bleeding decreased. This effect appeared to be dose related, with increasing LNG as in LCS16 and Mirena having greater effects.

- **Compliance**

Overall compliance (as defined via IUS location with ultrasound) was high in both studies in all treatment groups. Importantly there was no difference in correct position of the IUS was seen between parous and nulliparous women.

- **Early safety signals**

An analysis of the available return-to-fertility although early, was reassuring with 25 out of 29 women who discontinued study A46796 because of wish for conception becoming pregnant during the 12-month follow-up. Unintended pregnancy due to expulsion was uncommon although monitoring post registration would be important.

More than three quarters of women who completed the user satisfaction questionnaire were 'very satisfied' with study treatment.

Of note, almost all women are of Caucasian origin, and thus generalisability to other ethnic groups cannot be made. The LCS12 has met the CHMP criteria for effective contraception, discussed above, although this was not met for LCS16 in the Phase 2 study.

8. Clinical safety

Analysis of the safety of LCS12 is based on the same clinical studies, i.e. the pivotal phase 3 study A52238 and the comparative phase 2 study A46796, as for analysis of contraceptive efficacy.

Similarly, the same analysis set (FAS as defined above) was used for the safety and efficacy assessment and therefore characteristics of the study population have been discussed. Safety data were examined for each individual study and also for the pooled analysis.

All women who were enrolled and had an insertion attempt (both pivotal and supporting) were included in the safety analysis, including 1672 women assigned to LCS12, 1697 women assigned to LCS16, and 256 women assigned to Mirena (total women 3625).

Safety variables evaluated in these studies are:

- Concomitant medication
- Adverse Events (AEs) and serious adverse events (SAE) – number plus analysis by age, parity, ethnicity, BMI, and time. These included expulsion of the LCS, and pelvic inflammatory disease (PID). Ovarian cysts reported as AEs if they were abnormal non-functional cysts and/or had a diameter > 3 cm. Ectopic pregnancies and perforations were reported as SAEs in A52238 and A46976.
- Laboratory tests including pregnancy tests
- Vital signs
- General physical, breast, gynecological examinations, including vaginal and cervical smears and vaginal ultrasound (for A52238 and A46976)
- Cervical smear.

Safety variables of special interest are:

- ectopic pregnancy
- pelvic inflammatory disease (PID)
- IUS expulsions and perforations.
- IUS insertion/removal ease and pain,
- endometrial safety
- bone mineral density (a priori subgroup in study A52238 only).

Stratification by age, parity, and time is also undertaken.

In study A46796, some events such as including acne, bloating, breast pain, breast tension, oedema, headache, mood changes, nausea and weight gain) were classified as progestogenic-related side effects and assessed at every visit via specific questioning. In contrast, these events were recorded as reported voluntarily by the women in study A52238. This difference in AE reporting is likely to have contributed to a higher frequency of the side effects classified as progestin-related in study A46796 (67 to 72%) than in study A52238 (50 to 52%).

8.1.1. Pivotal studies that assessed safety as a primary outcome

There were no pivotal studies that assessed safety as a primary outcome.

The dose-response and non-pivotal efficacy studies A46076, A52238 and A229 provided safety data, covered in an Appendix not included in this Extract.

8.2. Patient exposure

Table 17. Mean exposure to LNG and comparators in clinical studies.

Study type/ Indication	Uncontrolled studies			Total LNG (all doses)
	LCS12	LCS16	Mirena	
Clinical pharmacology				
Treatment duration (days)	821	843		1664
Treatment duration (Women Years (wy))	2.25	2.31		2.56
Study A46796				
Treatment duration (days)	915	912	895	7722
Treatment duration (Women Years)	2.51	2.50	2.45	4.9
TOTAL wy (days)	**4.76 (1736)**	**4.81 (1755)**	**2.45 (895)**	**10.56 (9386)**

On average, the mean exposure for women on LCS12 in the youngest age group or nulliparous group was approximately 60 or 40 days shorter when compared to the overall population.

8.3. Adverse events

8.3.1. All adverse events (irrespective of relationship to study treatment)

8.3.1.1. Pivotal studies

Table 18. Adverse event profile – FAS, studies A52238 and A46796 combined

Study A52238			Study A46796		
	LCS12	LCS16	LCS12	LCS16	Mirena
n (%)	n (%)	n (%)	n (%)	n (%)	
Total of women	1432 (100%)	1452 (100%)	240 (100%)	245 (100%)	256 (100%)
Any AE	1194 (83.4%)	1246 (85.8%)	208 (86.7%)	220 (89.8%)	233 (91.0%)
Drug-related	710 (49.6%)	756 (52.1%)	162 (67.5%)	163 (66.5%)	184 (71.9%)
Maximum intensity					

Study A52238			Study A46796		
	LCS12	LCS16	LCS12	LCS16	Mirena
mild	313 (21.9%)	353 (24.3%)	53 (22.1%)	60 (24.5%)	51 (19.9%)
moderate	616 (43.0%)	633 (43.6%)	122 (50.8%)	121 (49.4%)	145 (56.6%)
severe	261 (18.2%)	250 (17.2%)	33 (13.8%)	37 (15.1%)	36 (14.1%)
Any Serious AEs (SAEs)	66 (4.6%)	71 (4.9%)	12 (5.0%)	12 (4.9%)	16 (6.3%)
Total deaths	0 (0.0%)	1 (<0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Drug-related SAEs	8 (0.6%)	15 (1.0%)	2 (0.8%)	3 (1.2%)	5 (2.0%)
Discontinuation due to AEs	319 (22.3%)	290 (20.0%)	42 (17.5%)	47 (19.2%)	48 (18.8%)
Discontinuation due to SAEs	14 (1.0%)	18 (1.2%)	1 (0.4%)	4(1.6%)	3 (1.2%)

8.3.1.2. Other studies

Nil.

8.3.2. Treatment-related adverse events (adverse drug reactions)

8.3.2.1. Pivotal studies

A52238 and A46796

In the pivotal study A52238, the most common AEs in the LCS12 group were ovarian cyst (13.0%), acne (11.4%), urinary tract infection (11.0%), headache (9.3%), dysmenorrhea (9.1%), cervical dysplasia (7.5%), bacterial vaginitis (7.3%), nasopharyngitis (7.2%), abdominal pain (7.0%), and vulvovaginal mycotic infection (6.9%). The most common AEs in A46796 are as per the table below. It can be seen that there is a higher frequency of 'progestogenic' AEs in study A46796 as compared to study A52238 probably because in A46796, these side effects were assessed at every visit via specific questioning (unlike voluntarily reporting in A52238).

Table 19. Most common AEs: Studies A52238 and A46796

	Incidence A52238 (%)	Incidence A46796 (%)
Ovarian cyst	13	8.8
Acne	11.4	26.7
Urinary Tract infection	11	9.2

	Incidence A52238 (%)	Incidence A46796 (%)
headache	9.3	26.3
Dysmenorrhoea	9.1	
Cervical dysplasia	7.5	
Bacterial vaginitis	7.3	
Nasopharyngitis	7.2	
Abdominal pain	7.0	
Vulvovaginal mycotic infection	6.9	9.6
Breast discomfort		21.7
Mood altered		17.9
Abdominal distension		16.7
Weight increased		15.8
Breast pain		8.3

Most common drug-related AEs by MedDRA preferred term

Drug-related AEs were defined as AEs for which the association with the investigational product (causality) was assessed by the investigator as 'missing', 'possibly', 'probably', or 'definitely' - related. The most frequently reported drug-related AEs are presented by MedDRA preferred terms:

Table 20. Most frequently reported drug-related AEs by MedDRA preferred terms

	A52238 (%)	A46796 (%)
Acne	10.1	25.8
Ovarian Cyst	7.7	5.8
Dysmenorrhea	6.8	
Pelvic pain	4.7	
Vaginal hemorrhage	4.5	
Abdominal pain	3.4	
Headache	3.3	11.7

	A52238 (%)	A46796 (%)
Weight increases		11.3
Breast discomfort		19.2
Altered mood		14.2
Abdominal distension		13.8

MedDRA classification with IUS

Adverse events specifically associated with an IUS include partial or complete expulsion, perforation or penetration of the uterine wall or cervix, embedment in the myometrium, an altered bleeding pattern. Therefore the following MedDRA primary System Organ Class (SOCs) is of interest for this application.

- Infections and infestations
- Neoplasms benign, malignant and unspecified (including cysts and polyps)
- Pregnancy, puerperium and perinatal conditions
- Reproductive system and breast disorders
- General disorders and administration site conditions
- Psychiatric disorders
- Vascular disorders

Infections and infestations are discussed here, the other SOCs are discussed in section 8.4.

Infections and Infestations

Urinary tract infection was the most common infection in both individual studies and in the pooled LCS treatment group data. In terms of SAEs, infections and infestations were reported for 54 total women overall (1.5%) - the most frequently reported were appendicitis, PID, pneumonia, pyelonephritis and urinary tract infection. Of specific clinical interest are PID and endometritis because of their effects on future fertility.

PID (as diagnosed by the investigator) was reported in approximately 0.4% of the women in the LCS treatment groups (FAS, pooled LCS12 and LCS16 data across studies A52238 and A46796). Most of the PIDs reported were serious, moderate to severe in intensity, related to study drug, occurred in parous women, and occurred during Year 1 of the study. Specifically, in the phase 3 study A52238, 12 cases were diagnosed with PID (6 in the LCS12 arm, and 6 in the LCS 16 arm). A total of 7 of these women (LCS12: 4, LCS16: 3) had an acute salpingo-oophoritis diagnosed and 3 (LCS12: 2, LCS16: 1) a tubo-ovarian abscess (women may have had one or both of these terms reported). Six of these were reported as SAEs relating to PID (2 in LCS12, and 4 in LCS16). In the phase 2 study A46796, two SAEs relating to PID in two women were reported: one in the LCS 16 arm and one with Mirena.

Endometritis A total of 0.8% of women in the LCS12 and LCS16 arms in study A52238, and 0.5% of the women in study A46796 were diagnosed with endometritis. Due to this AE, a total of four of the 26 women (15%) with endometritis were withdrawn from the studies. No cases of endometritis were classified as serious.

Presentation of undesirable effects in proposed Summary of Product Characteristics [equivalent to the proposed Product Information] for LCS12

The frequency estimate of an event to be included in the undesirable effects section was based on the number of all AEs that were reported for the respective MedDRA Labeling Grouping or preferred term (regardless of the causality assessment of investigators). A separate Justification Document for the table of Undesirable Effects of LCS12 based on this method was provided in the submission.

8.3.2.2. Other studies

Nil.

8.3.3. Deaths and other serious adverse events (SAE)

8.3.3.1. Pivotal studies

There was one death in study A52238, a suicide in a 20 year-old woman. This was attributed to depression and an eating disorder, assessed as unrelated to treatment. A narrative description of the case was provided which was satisfactory.

Overall, the frequency of drug-related SAEs (as assessed by the investigator) was very low - the most common were ectopic pregnancies, ovarian cysts, and PID.

The most frequent SAE in study A52238 was appendicitis for the LCS12 group and ectopic pregnancy/ruptured ectopic pregnancy for the LCS16 group, while in study A46795 it was ovarian cysts in the Mirena group. In the pooled analysis, SAEs were reported for 4.7% of women in the LCS12 (Jaydess) treatment group, 4.9% of women in the LCS16 group, and 6.3% of women in the Mirena group. Overall the most frequent SAEs were appendicitis (16 women), ectopic pregnancy (13), ovarian cysts (includes hemorrhagic, ruptured ovarian cysts, ovarian cyst torsion) (12), abdominal pain (10), and PID (8).

Table 21. Most frequent serious adverse events (SAEs) – FAS, studies A52238 and A46796

	A52238		A46796		
	LCS12	LCS16	LCS12	LCS16	Mirena
	n (%)	n (%)	n (%)	n (%)	n (%)
Total	1432 (100)	1452 (100)	240 (100)	245 (100)	256 (100)
Any SAE	66 (4.6)	71 (4.9)	12 (5.0)	12 (4.9)	16 (6.3)
Appendicitis	6 (0.4)	7 (0.5)	0 (0)	1 (0.4)	2 (0.8)
Ectopic pregnancy	3 (0.2)	7 (0.5)	1 (0.4)	2 (0.8)	0 (0)
Ovarian cyst	4 (0.3)	3 (0.2)	0 (0)	0 (0)	5 (2.0)
Abdominal pain	5 (0.3)	4 (0.3)	0 (0)	0 (0)	1 (0.4)
Abortion spontaneous	3 (0.2)	2 (0.2)	0 (0)	2 (0.8)	0 (0)
Pelvic inflammatory disease	2 (0.1)	4(0.3)	0 (0)	1 (0.4)	1 (0.4)

8.3.3.2. Other studies

No other deaths were reported in the clinical development program of LCS12.

8.3.4. Discontinuation due to adverse events

8.3.4.1. Premature discontinuations

There were a large number of discontinuations – approximately 40% in A52238 and approximately 30% in A46796 in both studies, due predominantly to AEs and 'other'. Approximately 20% of all women using LCS12 discontinued in both A52238 and A46796 due to AEs. Approximately 30% of those women who discontinued had "other" reasons for premature discontinuations, including a large number of women who wished for pregnancy, and smaller numbers who had no further need for contraception or who could not attend visits.

8.3.5. Other - IUD specific, other gynaecological, bone mineral density

8.3.5.1. IUD Specific

Both partial and total expulsion rates were very low in all treatment groups of both studies, however as not all expulsions were reported as AEs, the frequency of expulsion in the AE data is less than the actual expulsion data. Expulsions occurred at various times during the study treatment period with no trend detectable.

Table 22. Summary of expulsions

	LCS12 total (partial) expulsion	LCS16 total (partial) expulsion
A52238	29 (24)	16 (30)
A46796	0 (1)	3 (2)
Pooled analysis	3.98% for total or partial at 36 month	3.37% for total or partial at 36 month

A trend toward more partial and total expulsions was found in parous as compared to nulliparous women and in women ≤ 25 years as compared women 25 to 35 years.

- **Perforation**

A uterine perforation occurred in one woman in the LCS16 group in both studies combined. At the time of the submission, one additional partial perforation had occurred in the ongoing extension phase of the LCS16 group and one in the ongoing extension study (91775) (this occurred during uterine sounding prior to LCS insertion).

- **Insertion ease and pain**

Insertion was successful in 3609/3625 women (99.6% of women) in both studies. It was easier in parous women and with increasing age. The most frequent reasons for the failure of the first insertion were that the IUS came out immediately after insertion, or malfunction of the inserter. Local anesthesia or analgesics were given to a minority of women for the IUS insertion procedure. More nulliparous women received local anesthesia or anesthetics than parous.

The investigators assessed the insertion procedure of the LCS IUS as easy in approximately 90% of women. The investigator assessed the removal of the IUS as 'easy' in 1799/1993 women in study A52238 (90.3%) and as 'easy' in 499/552 women (90.4%) in A46796. Removal was assessed as 'very difficult' in approximately 2 % of all women.

In both studies, over 80% of the women experienced no or only mild pain on removal of the IUS (study A52238, 36.1% overall no; 45.9% mild; study A46796, overall 44.2% no, 38.8% mild). Nulliparous women experienced more pain during removal than parous women.

Most of the women in the clinical studies experienced no pain or only mild pain during the insertion of the IUS. Women in the LCS groups experienced less pain than those in the Mirena group as did parous women compared to nulliparous. Insertion pain lessened with increasing age.

- **Ectopic pregnancy**

In study A52238, a total of 20 pregnancies were observed under treatment; 10 in each treatment group. Of these, 3 in the LCS12 group (30%) and 7 in the LCS16 group (70%) were ectopic.

In study A46796, 6 pregnancies were observed during treatment: 1 (an ectopic pregnancy) in the LCS12 group and 5 in the LCS16 group (2 ectopic, 2 ended in spontaneous abortion and one the result of an unnoticed expulsion.

For the SOC Pregnancy, puerperium, and perinatal conditions, there were 20 total SAEs (0.6%); most frequently reported were ectopic pregnancy (0.3% overall) and spontaneous abortion (0.1% overall). Using the pooled data, the overall incidence of ectopic pregnancy was 0.11 per 100 wy for LCS12 and 0.24 per 100 wy for LCS16.

8.3.5.2. Gynecological examination findings

- **Cervical smears**

The majority of the epithelial cell abnormalities in both studies at screening, during the study (for study A52238 only) and at the end of the studies were atypical squamous cells of undetermined significance (ASCUS) and squamous intraepithelial lesions. This is also covered below in section 8.4.

- **Ovarian cysts**

In both A52238 and A46796, ovarian findings were normal in 95% women at all vaginal ultrasound examinations. The incidence of ovarian cysts at baseline in study A52238 (12.1 to 13.2%) was higher than that seen in study A46796 (1.6 to 2.1%) and higher than has been reported in the literature, possibly due to over-reporting of follicles as cysts.

- **Fibroids**

Overall, fibroids were demonstrable in ≤ 3% of women at baseline, throughout the study, and end of study in both studies. LCS12 had no apparent effect on fibroids.

- **Endometrial findings**

Overall, >99% of women had normal endometrial findings at screening, baseline, throughout the study, and end of study in both studies.

8.3.5.3. Bone mineral density

There was a slight increase in mean bone mineral density at both anatomic sites at all three post-baseline visits in both treatment groups, but of probable lack of clinical relevance. No difference was seen between the two treatment groups.

8.4. Laboratory tests

8.4.1. Liver function

8.4.1.1. Pivotal studies

The results of general safety laboratory evaluations for LCS12 (Jaydess), including general chemistry, liver function, lipid and carbohydrate parameters and urinalysis in the two studies (A52238 and A46796) were generally unchanged from baseline. There were no concerns with

the clinical chemistry data. Importantly, the studies did not examine the use of Jaydess in women with impaired liver function so this data is unknown.

8.4.2. Kidney function

8.4.2.1. Pivotal studies

The results of general safety laboratory evaluations for LCS12 (Jaydess), including general chemistry, liver function, lipid and carbohydrate parameters and urinalysis in the two studies (A52238 and A46796) were generally unchanged from baseline. There were no concerns with the clinical chemistry data. Importantly, the studies did not examine women with impaired renal function so this data is unknown.

8.4.3. Other clinical chemistry

8.4.3.1. Other studies

A Cochrane Review (2010) has shown that the LNG-20 IUS (higher release rate than Jaydess) does not have an adverse effect on glucose metabolism among insulin-dependent diabetic women (6).

8.4.4. Haematology

8.4.4.1. Pivotal studies

Haematology parameters showed no significant differences between the treatment groups in the respective studies A52238 and A46796 and raised no concern.

8.4.5. Vital signs

8.4.5.1. Pivotal studies

In both A52238 and A46796 studies, there was no relevant change from baseline to end of study in mean weight, mean systolic blood pressure, mean diastolic blood pressure, or mean heart rate.

8.4.6. Neoplasms, benign, malignant and unspecified (including cysts and polyps)

Adverse events for the SOC Neoplasms, benign, malignant and unspecified were uncommon. The most frequently reported neoplasms overall were uterine leiomyoma, vulvovaginal human papilloma virus infection, melanocytic naevus, fibroadenoma of the breast, and ovarian germ cell teratoma benign. SAEs were reported for 17 total women (0.5%); these included ovarian germ cell teratoma benign (0.1% overall); and thyroid cancer (<0.1% overall).

8.4.7. Reproductive system and breast disorders

The most frequently reported Reproductive system and breast disorders were ovarian cyst, dysmenorrhea, and cervical dysplasia. The relatively high number of ovarian cysts documented and reported as AEs are likely to be a result of the frequent ultrasound examinations mandated in the study protocols. Specifically, the overall frequency when combining the MedDRA relevant preferred terms for ovarian cyst (ovarian cyst, ruptured ovarian cyst, hemorrhagic ovarian cyst, ovarian cyst torsion) in the pooled data was 13.2%, 20.1%, and 25.0%, in LCS12, LCS16, and Mirena groups, respectively.

Over 98% of the ovarian cysts reported in the LCS treatment groups were not serious and did not result in study drug discontinuation. However in A52238, study treatment was withdrawn in 8 women (three in the LCS12 group, and five in the LCS16 group). Ovarian cysts were reported as SAE in 7 women (4 in the LCS12 group, and 3 in the LCS16 group). Five of these women underwent laparoscopic procedures and 2 were treated medically.

In study A46796, study treatment was withdrawn due to the event in 5 women in the Mirena group, one in the LCS12 group, and two in the LCS16 group. Ovarian cysts were reported as

SAEs in 5 women in the Mirena group but none of the women in the LCS groups had an ovarian cyst reported as SAEs (one dermoid cyst was reported in the LCS12 group).

Cervical dysplasia was reported in 7.7% of women in study A52238 and 3.3% in study A46796. Most events were not serious and did not result in discontinuation of study drug. These were classified as 110 cases of cervical low-grade squamous intraepithelial lesions (LGSIL), 87 cases of atypical squamous cells of undetermined significance (ASCUS), and 33 cases of high-grade squamous intraepithelial lesions (HGSIL). For >93% of women cervical smears were normal for all treatment groups at screening and at all time points of both studies.

8.4.8. General disorders and administration site conditions

The most frequently reported General disorder and administration site condition was device expulsion. In the pooled data of study A52238 and study A46796, there were 54 expulsions (3.2%) in the LCS12 group. There was one perforation with LCS16 in the extension phase of A52238. There was one additional perforation during sounding in the LCS12 group in the Asian/Pacific study – prior to LCS12 being inserted. This subject was withdrawn from the study.

8.4.9. Psychiatric disorders

In the SOC Psychiatric disorders, SAEs were reported in 0.2% women, which included depression (<0.1% overall) and anxiety (<0.1% overall). There was one woman in the LCS12 group with an SAE of depression and a suicide attempt (unsuccessful) and one woman in the LCS16 group with a completed suicide (SAE outcome fatal). Neither of the latter two cases was assessed as drug-related however. Overall the most frequent psychiatric AE reported in study A46796 was altered mood (with depression reported in 13 women (5.4% in LCS12), 6 women (2.4% in LCS16) 10 women (3.9% in Mirena) and 29 (3.9% total). The most frequent psychiatric AE (345 women, 12%) reported in study A52238 was depression (3.5%).

8.4.10. Vascular disorders

There were a small number of vascular events and there were 2 SAEs - deep vein thrombosis occurring in the setting of plane travel (1), and hypertension (1).

8.4.11. Analysis of subgroups for adverse events

Adverse events were analysed by age (18 to 25 years, 26 to 35 years, and over 35 years), ethnicity subgroup (Caucasian, Black, Hispanic, Asian, and Other), parity, and BMI. In general, there were no overall trends that were not reflected by the study population taken as a whole but some of the subgroups were small.

8.5. Post-marketing experience

No post-marketing data are available for LCS12 because this product has not yet been marketed. However post-marketing safety data for Mirena, Bayer's marketed LNG-IUS that has an initial release rate of approximately 20 μg/day and a 5 year period of use, are available, and a large active post-marketing surveillance and research (Phase 3b) program is ongoing. In the latest Periodic Safety Update Report (PSUR) for Mirena, there was no evidence of any new safety concerns.

In the submission, reference is made to the safety experience from Mirena.

8.6. Other safety issues

8.6.1. Safety in special populations

In the pivotal and supporting trials there were no additional safety concerns in any subpopulation of women. Specifically, adverse events were analysed by age subgroup (18 to 25 years, 26 to 35 years, and over 35 years), ethnic subgroup (Caucasian, Black, Hispanic, Asian,

and Other), parity, and BMI. In general, there were no overall trends that were not reflected by the study population taken as a whole, although some of the subgroups (e.g. ethnicity) were small. More AEs overall were reported in the 18 to 25 year age group, and in nulliparous women.

8.6.2. Safety related to drug-drug interactions and other interactions

There were no drug interaction studies.

8.7. Evaluator's overall conclusions on clinical safety

The safety of the LCS12 IUS was evaluated in 1672 women in good general health seeking contraception over a three-year time point. An additional 1697 women were studied with the slightly higher release LCS16, and 256 with the higher dose Mirena.

The overall clinical safety profile of LCS observed (from the A46796 and A52238 studies) gave no new safety concerns that are not already known from the surveillance and clinical trial data from other IUSs and other LNG preparations. Specifically, many of the common AEs were similar to those that are known to occur with other LNG preparations (acne, ovarian cyst, dysmenorrhea) were seen. The short-term presented data do not indicate an increased risk of venous thromboembolism, cardiovascular events nor cancer incidence.

In the pooled analysis, SAEs were reported for 4.7% of women in the LCS12 (Jaydess) treatment group, 4.9% of women in the LCS16 group, and 6.3% of women in the Mirena group. Overall the most frequent SAEs in descending order were: appendicitis, ectopic pregnancy, ovarian cysts, abdominal pain and PID. The pooled incidence of PID in the LCS12 and 16 arms across A46976 and A52238 was approximately 0.4 % with an incidence of 0.11 per 100 wy. The incidence of endometritis was 0.8% in pooled LCS12 and LCS16 data in A52238.

In terms of ectopic pregnancy the absolute risk with LCS12 is less than in non-contraceptive users (estimated ectopic rate of approximately 0.3 to 0.5 per 100 wy cf. 0.11 per 100 wy with LCS12, similar to the rate in the Mirena clinical studies).

Approximately 50% women had any drug related AE, with 8-26% in A46976 complaining of one or more 'progestogenic' side effects. There were a large number of discontinuations – with approximately 20% of all women using LCS12 discontinuing use due to AEs. The most common ones were vaginal hemorrhage, device expulsion (3.2% at 36 months with Jaydess) and acne. There was a trend toward more partial and total expulsions in parous as compared to nulliparous women in subgroups analysis in both studies. In subgroups of women evaluated there were no clear safety issues although some (including the BMI>30kg/m^2 and some ethnic groups) were small.

There have been 2 perforations, one in the LCS16 (not Jaydess) group and 1 in the LCS12 group during sounding, in the Asia-Pacific study. Also, psychiatric SAEs were reported in 0.2% women, which included depression (<0.1% overall) and anxiety (<0.1% overall). Depression as an AE was reported in 5.4% (LCS12), 2.4% (LCS16) 3.9% (Mirena) and 3.9% (total in A46976). The most frequent psychiatric AE (incidence of 12%) reported in study A52238 was depression (3.5%).

Further, although over 98% of the ovarian cysts reported in the LCS treatment groups were not serious and did not result in study drug discontinuation, study treatment was withdrawn in 8 women (three in the LCS12 group, and five in the LCS16 group) in A52238, and ovarian cysts were reported as SAE in 7 women (4 in the LCS12 group, and 3 in the LCS16 group). Five of these women underwent laparoscopic procedures and 2 were treated medically.

Lastly, removal was assessed as 'very difficult' in approximately 2 % of all women.

So safety concerns recommended to be addressed are:

- highlighting that many women get progestogenic side effects
- whilst the rate of ectopic pregnancy is less than in the general population, the likelihood of a pregnancy, if it occurs, being ectopic is higher. The Sponsor is considering the feasibility of a prospective database study to address this risk of ectopic pregnancy in LCS12 users in the market and this is supported. The proposed label for LCS12 is to include a warning on the risk, and signs and symptoms of ectopic pregnancy although this is not evidence in the labelling submitted in Module 1. The company further proposes to explore options to make the patient information accessible through additional channels, e.g. the internet, as a means of further risk minimization and this is supported although evidence that this is underway is needed
- although incidence of PID and endometritis is uncommon (<1/100), it did occur in the clinical trials and [it is important] to note that Jaydess does not protect against STDs. It is noted that the Sponsor has stated that it is evaluating additional pharmacovigilance activities and educational programmes to reduce the incidence
- partial or complete IUD expulsion is a risk with Jaydess, which may be higher in the non-trial setting where IUS position is not checked routinely after insertion – between 1-10%
- perforation is rare, has not been seen with Jaydess but has occurred with a similar IUS. The Sponsor has a planned educational program for LCS12 to emphasise correct insertion technique to reduce the risk of incorrect placement or perforation
- ovarian cysts whilst common in this population may cause complications
- depression and anxiety are common in this age group but there was an prevalence of 3% of these conditions in this study and awareness of this by the woman and the prescriber is important

There were no safety concerns in laboratory variables, vital signs, and other safety parameters observed. The overall incidence of new abnormal endometrial or cervical findings was low. There was no negative effect on bone mineral density.

In summary, there appears to be no new safety concerns with LCS 12, compared to Mirena and other IUSs. However, the rate of ectopic pregnancies, PID and expulsions needs to be observed. Ongoing observational data in a subgroup of obese women (BMI>35) should also be provided in the PSUR.

9. First round benefit-risk assessment

9.1. First round assessment of benefits

The benefits of Jaydess in the proposed usage are:

- Effective long-term contraception- the unadjusted PI for LCS12 for the first year was 0.41, and upper limit of the 2 sided CI is 0.96
- Reduced menorrhagia (prolonged and heavy bleeding) and intracyclic bleeding
- Less daily release rate of LNG than comparator IUS LNG product
- 'Easy' to insert for most nulliparous women, but no comparison data with other IUDs or standard
- Theoretically LCS12 efficacy is unlikely to be impacted by the use of co-medications that induce cytochrome P450 enzymes although evidence is lacking.

9.2. First round assessment of risks

The risks of Jaydess in the proposed usage are:

- Possible long-term fertility issues due to ectopic pregnancy, PID, endometritis, expulsions
- Possible unintended pregnancy due to partial or total expulsion
- Progestogenic side effects

9.3. First round assessment of benefit-risk balance

The benefit-risk balance of Jaydess given the proposed usage is favourable for women aged 18-41 requesting long-term contraception with an IUD. The Sponsor's proposed pharmacovigilance and education programs around this product are recommended to be mandatory.

10. First round recommendation regarding authorisation

Recommendation is to recommend registration with an ongoing pharmacovigilance report, particularly on the risk of expulsions, ectopic (and normal) pregnancy, and rate of pelvic inflammatory disease.

In relation to the *Indications* in the proposed PI (120813 version):

The proposed indication has been amended [by the sponsor] from "Contraception for up to three years" to "Contraception". It is recommended to return the indication back to the original "Contraception for up to 3 years" from 'Contraception" (under 'Indication') so it is clear this is not a temporary form of contraception that could be stopped and started. It also reminds women that after three years the IUS should be removed and a new method is required.

[Note: additional recommendations regarding revisions to the PI and comments on the draft CMI are not included in this Extract from the CER].

11. Clinical questions

11.1. Pharmacokinetics

Nil required.

11.2. Pharmacodynamics

Nil required.

11.3. Efficacy

Are there any additional relevant data from long term follow-up or extension of the pivotal studies?

11.4. Safety

Up to date information on the other (non-TGA) jurisdictions for Jaydess registration was not provided at the time of the submission.

Is there up to date registration information?

1. Are there any additional relevant data from long term follow-up or extension of the pivotal studies?
2. Other studies mentioned in the dossier included:
   - Study 91775
   - Study 13362.
   - A phase 3b (protocol 13363)

Are there additional safety data from these studies, particularly with respect to ectopic pregnancy, expulsion, and infection, available for evaluation?

12. Second round evaluation of clinical data submitted in response to questions

In the S31 replies, the Sponsor has submitted extra information for Modules 1,3 and 5 and provided some data (when available) on the long-term extension studies.

Module 1 includes Table of Contents, EU Risk Management Plan and Plan for Australia, label mockups and specimens, proposed CMI and PI (the latter with tracked changes), responses to questions, letter of application and Table of Contents.

Module 3 includes Table of Contents, documentations about reference standards and stability data.

Module 5 includes Table of Contents, Clinical Study Report for 91665 and its amendment for the follow up of the 'return to fertility'.

The below TGA questions (**in bold**) and answers (Sponsor) are those that specifically relate to the clinical questions and those posed by the First Round Evaluation. They are taken from Module 1.0.2 Responses to Questions from the request for information from the Module 5 Evaluator.

12.1. Efficacy

Are there any additional relevant data from long term follow-up or extension of the pivotal studies?

The ongoing extension phase of the pivotal Phase 3 study (Protocol 310442-91665, Report A52238) includes only subjects in the LCS16 group who were given the option to continue use up to a maximum of 5 years of treatment according to Protocol Amendment 5 of this study. There had been one addendum to the Phase 3 study relating to the follow-up of return to fertility information gathered after completion of the 3 year phase of the study. This addendum was finalised on 27 Feb 2013 and the appendices to the addendum are provided electronically and reviewed. In this extension study, 204 women who wished to become pregnant were followed up; 76.7% of these became pregnant in 1 year. This is comparable with return to fertility data for users of IUSs with higher dose LNG. The health outcomes apart from expulsions in the women who had continued was unable to be located.

There was no long-term follow-up from the completed Phase 2 study (Protocol 308901, Report A46796). There had been one amendment to the Phase 2 study which was reviewed in the initial evaluation (analysis of bleeding patterns, return to fertility and PD, collected after the study was completed).

The Sponsor advises that there are currently 4 studies ongoing with Jaydess and the estimated reporting timelines for these are in the latter half of 2013 (Q3 and Q4) and 2014 (Q1).

12.2. Safety

Up to date information on the other (non-TGA) jurisdictions for Jaydess registration, with noted approval in the USA and Sweden in 2013.

- The Netherlands Submitted December 2011
- United Kingdom Submitted December 2011
- Switzerland Submitted January 2012
- Canada Submitted April 2012
- United States of America Approved 9 January 2013
- Sweden Approved 10 January 2013
- New Zealand To be submitted

Additional safety data from

- Study 91775
- Study 13362A
- Phase 3b (protocol 13363), was requested, specifically on ectopic pregnancy, expulsion, and infection.

Appendix 1 in the Response provided a tabular listing of pregnancies, expulsions, PID reported and SAEs (up to a cut-off date of 23 December 2012) in the ongoing Jaydess studies. It was noted that this data is from ongoing studies where no formal data cleaning has taken place and therefore cannot be considered final data. These studies include: Protocol 91775; Protocol 13362; Protocol 13363; and Protocol 14371;

Pregnancies:

Protocol 91775: In 918 women with successful insertions there were 8 on-treatment pregnancies, which with a 2150 WY gives a Pearl index of 0.37. Of these pregnancies, 2 x unnoticed LCS expulsion, 1 x displaced LCS12, 4 ectopics, one pregnancy whilst LCS 12 *in situ.*

Protocol 13362: 1 ectopic pregnancy, 1 spontaneous abortion.

Protocol 13363: 1 ectopic and 1 with LCS *in situ* (difficult history).

Protocol 14371: No on-treatment pregnancies were reported.

For studies 13362, 13363, 14371 the number of successful insertions and WY was not provided to enable calculation of PI.

Deaths:

2 deaths judged as unrelated to LCS12.

SAEs reported up to Dec 2012 and judged by investigator/Sponsor to be related to IUS:

91775: Ovarian torsion, vulvovaginitis, ectopic (3), ovarian cyst (3).

13362: 1 ectopic, 1 spontaneous abortion, ovarian cyst.

13363: 1 ectopic, 1 cerebral infarction (not LCS12 group).

14371: 1 each of endometritis, ovarian torsion, abdominal pain, pelvic pain, ovarian cyst.

Expulsions:

91775 – as of the cutoff date, 40 total or partial expulsions have been reported in which a total of 918 subjects underwent successful LCS12 insertions. This gives a crude incidence of expulsion of 4.4%, similar to the incidence in the A52238 in which there was expulsion of 3.7%

in the LCS12 and 3.4% in the LCS16 group. The Sponsor suggests that as the expulsion rate was higher in the parous than nulliparous women, and as 91775 has proportionally more parous women that this could explain the slightly higher expulsion rate.

13362: No partial or complete expulsions reported as of Dec 2012.

13363: As of cutoff date, 4 expulsions out of 378 successful insertions giving a crude incidence of 1.1%.

14371: As of the cutoff date for this report there had been 10 partial or total expulsions out of a total of 303 women with successful insertions.

Perforations:

In the A52238 LCS16 extension, there has been two further partial perforations, with removal of the LCS without complications. One perforation during sounding of the uterus in **91775**, but no others in **13362, 13363** and **14371.**

Pelvic inflammatory disease:

91775 – the crude incidence of upper genital infection is 10/925 subjects with insertion (cf. 1.4% in A55238). Nil were SAEs and all have recovered, although long-term data regarding fertility will not be available for several years.

13362: One endometritis.

13363: One salpingitis.

14371: 2 endomyometritis, 2 endometritis.

Overall, these rates are similar to the pivotal A52238, and there were no new events reported.

13. Second round benefit-risk assessment

13.1. Second round assessment of benefits

After consideration of the responses to clinical questions, the benefits of Jaydess in the proposed usage are unchanged from those identified in Section 9.1.

13.2. Second round assessment of risks

After consideration of the responses to clinical questions, the benefits of Jaydess in the proposed usage are unchanged from those identified in Section 9.2.

The risks of Jaydess in the proposed usage are:

- ectopic and intra uterine pregnancy
- expulsion of IUD
- infection

13.3. Second round assessment of benefit-risk balance

The benefit-risk balance of Jaydess given the proposed usage is favourable on a population basis. However there is a risk to future fertility particularly in nulliparous women due to the rate of ectopic pregnancies and PID, and the pharmacovigilance plans as assured by the Sponsor need to be mandated for this product. Further, information about long-term outcomes and real world practice needs to be communicated to prescribers and regularly updated. Specific data on

obese women, parous and nulliparous needs to be provided, particularly around expulsions, PID, pregnancies (both ectopic and intrauterine).

Further:

- PASS protocol needs to be included in Annex 5 of the EU-RMP as assured by Sponsor.
- Pharmacovigilance activities as discussed in the response are mandated to occur and are communicated to the TGA.
- If the results from the insertion survey are not directly applicable to Jaydess then the Sponsor needs to have considered an alternative education and training plan.
- Bayer provides the assurance that the printed materials associated with these risk minimisation activities will be provided to TGA, once available.
- The Sponsor states in the Return to Fertility addendum for the Phase 3 study (ph 37039 report) that no other post treatment information is provided in the 707 women who entered the LCS16 extension study of A52238. However there is noted that there were 2 further partial perforations in A52238 in the LCS16 arm. If there is further outcome data on this 'extension' group of A52238 this is important to Review.

14. Second round recommendation regarding authorisation

Recommend listing with pharmacovigilance and education strategies as assured by Sponsor.

15. Comments on clinical aspects of the Safety Specification in the draft RMP

The Sponsor provided new clinical information after the first round and revised the Safety Specification in the draft RMP. The clinical evaluator's comments on proposed post-market activities were referred to the TGA Office of Product Review (RMP evaluator). Details of these comments are not included in this Extract from the CER.

16. References

1. Committee for Medicinal Products for Human Use (CHMP) 'Guideline on Clinical Investigation of Steroid Contraceptives in Women' (EMEA/CPMP/EWP/519/98 Rev 1 July 2005) <http://www.emea.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003349.pdf> (accessed December 15, 2012)
2. REGULATION (EC) No 1901/2006 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 12 December 2006 on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004 <http://eurlex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2006:378:0001:0019:en:PDF> (accessed and checked Dec 15, 2012)
3. Ronit Haimov-Kochman, Hagay Amsalem, Amiram Adoni, Yuval Lavy and Irving M. Spitz Management of a perforated levonorgestrel-medicated intrauterine device—a pharmacokinetic study: Case report. Human Reproduction. Vol 18(6) 12310-1233
4. (<http://www.medsafe.govt.nz/profs/puarticles/lactation.htm>) accessed Dec 15, 2012

5. Heikkila M. Puerperal insertion of a copper-releasing and a levonorgestrel-releasing intrauterine contraceptive device. Contraception 1982;25:561–57

6. <http://www.thecochranelibrary.com/userfiles/ccoch/file/Intrauterine%20devices/CD001776.pdf> accessed Dec 15, 2012

7. Belsey EM, Machin D, d'Arcangues C. The analysis of vaginal bleeding patterns induced by fertility regulating methods. World Health Organization Special Programme of Research, Development and Research Training in Human Reproduction. Contraception 1986;34(3):253–260

Other reference consulted: FDA guidance on 'Extended Release Oral Dosage Forms: Development, Evaluation, and Application of *In vitro*/*In vivo* Correlations' (module 5.4 FDA Sep 1997) and of the Committee for Proprietary Medicinal Products (CHMP) 'Note for Guidance on Quality of Modified Release Products: A: Oral Dosage Forms, B: Transdermal Dosage Forms, Section I (Quality)' (module 5.4 CHMP 1999).

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