Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for Levonorgestrel IUS

Proprietary Product Name: Kyleena

Sponsor: Bayer Australia Ltd

First round CER: July 2016

Second round CER: September 2016

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.
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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 <https://www.tga.gov.au/product-information-pi>.

Contents

List of abbreviations

Abbreviation	Meaning
AE	Adverse event
$AUC_{(0\text{-}tlast)}$	Area under the drug concentration versus time curve from time 0 until removal of the IUS at 5 years after insertion
BMI	Body mass index
C_{av}	Average steady state concentration ($AUC_{(0\text{-}tlast)}/t_{last}$)
CCDS	Company core data sheet
CER	Clinical evaluation report
CI	Confidence interval
CL/F	Apparent clearance
C_{last}	Last observed concentration
C_{max}	Maximum observed concentration
CMI	Consumer medicine information
C_{min}	Minimum observed concentration
CSR	Clinical study report
CV	Coefficient of variation
DLP	Data lock point
EU	European Union
FAS	Full analysis set
IUS	Intrauterine delivery system
LARC	Long-acting reversible contraceptive
LNG	Levonorgestrel
MedDRA	Medical Dictionary for Regulatory Activities
PI	Pearl Index
PK	Pharmacokinetic

Abbreviation	Meaning
PSUR	Periodic safety update report
PT	Preferred term
SmPC/SPC	Summary of product characteristics
SOC	System organ class
SHBG	Sex hormone binding globulin
TEAE	Treatment-emergent adverse event
t_{last}	Time to reach C_{last}
t_{max}	Time to reach C_{max}
t_{min}	Time to reach C_{min}
WHO	World Health Organization
WY	Woman-years

1. Introduction

This is a submission to register Kyleena, a new strength levonorgestrel (LNG) containing intrauterine drug delivery system (IUS).[1] This product is comparable to the registered products Mirena (an IUS containing 52 mg LNG), the initial IUS of this type, and Jaydess (an IUS containing 13.5 mg LNG), which is registered in Australia but not marketed.

1.1. Drug class and therapeutic indication

Levonorgestrel is a second generation progestin with known anti-proliferative effects on the endometrium. LNG is used widely as the progestogenic component of combined oral contraceptive pills, as well as progestogen only pills and intrauterine drug delivery systems.

The proposed indication is:

'Contraception for up to 5 years'.

Comment: The proposed indication differs from the current approved indications for Mirena and Jaydess, which are as follows:

The approved indication for Mirena is:

'Mirena is indicated for:

- *Contraception*
- *Treatment of idiopathic menorrhagia*
- *Prevention of endometrial hyperplasia during oestrogen replacement therapy'.*[2]

The approved indication for Jaydess is:

'Contraception for up to 3 years'.[3]

1.2. Dosage forms and strengths

The following dosage forms and strengths are currently registered:

- Mirena levonorgestrel 52 mg intrauterine drug delivery system sachet AUST R 73027
- Jaydess levonorgestrel 13.5 mg intrauterine drug delivery system sachet AUST R 200456

The submission proposes registration of the following dosage forms and strengths:

- Kyleena levonorgestrel 19.5 mg intrauterine drug delivery system.

[1] This application was originally submitted by the sponsor under the tradename Sofitta. Following the first round evaluation, at the request of the sponsor, the proposed tradename changed from Sofitta to Kyleena. For continuity and clarity, Kyleena is used throughout this document except where discussion of any changes in tradename may be relevant to the evaluation itself.

[2] Australian PI for Mirena levonorgestrel 52 mg intrauterine drug delivery system sachet. Bayer Australia Ltd

[3] Australian PI for Jaydess levonorgestrel 13.5 mg intrauterine drug delivery system sachet. Bayer Australia Ltd

1.3. Dosage and administration

The proposed dosage and administration for Kyleena is:

'Kyleena is inserted into the uterine cavity and is effective for up to five years'.

Further information is provided regarding in vivo release rates, failure rates, medical examination/consultation, insertion and removal/replacement of Kyleena.

2. Clinical rationale

Kyleena is a low dose LNG IUS which has been developed for use as a long acting reversible contraceptive (LARC). There are two LNG IUS currently registered. The Mirena IUS contains 52 mg of LNG with initial in vitro release rate of 20 µg/24 hours and can be used for up to five years. Jaydess (designated LCS12 during development) is a lower dose LNG IUS containing 13.5 mg of LNG with initial in vitro release rate of 12 µg/24 hours. Jaydess can be used for up to 3 years.

The current submission proposes to register Kyleena (designated LCS16 during development), a low dose IUS containing 19.5 mg of LNG with initial in vitro release rate of 16 µg/24 hours. The proposed duration of use is for up to five years. The sponsor's rationale is '*the smaller size of LCS16 as compared with Mirena has been designed to facilitate successful insertion in a wide range of women. The treatment duration of up to five years with LCS16 is considered to be a suitable option for women who would prefer the smaller insertion tube diameter and lower dose (compared to Mirena) but are interested in a 5 year treatment option (compared to LCS12)*'.

The sponsor's rationale is considered acceptable.

2.1. Guidance

The TGA adopted EU Guideline on Clinical Investigation of Steroid Contraceptives in Women (EMEA/CHMP/021/97 Rev.1) was available.

3. Contents of the clinical dossier

3.1. Scope of the clinical dossier

The submission contained the following clinical information:

- 3 clinical pharmacology studies
- 8 population pharmacokinetic reports
- 1 pivotal efficacy/safety study
- 5 other efficacy/safety studies
- 1 PSUR
- A Clinical Overview, Summary of Clinical Efficacy, and Summary of Clinical Safety.

Comment: The majority of submitted data has been evaluated previously in the submission for Jaydess.[4] The focus of this report will be the pivotal efficacy/safety

[4] AusPAR for Jaydess (intrauterine delivery system) levonorgestrel Bayer Australia Ltd; February 2014. TGA; Canberra, Australia.

Study 91665/310442 supporting use of Kyleena for up to 5 years, and additional safety data from 4 studies with Jaydess.

3.2. Paediatric data

The TGA paediatric development program form states data to support use in the paediatric population was not submitted. On review of the dossier, data for adolescent subjects has been submitted. The sponsor is asked to comment why this was not indicated as such on the application form.

3.3. Good clinical practice

The clinical expert stated all clinical studies performed in the framework of this submission were conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice.

4. Pharmacokinetics

4.1. Studies providing pharmacokinetic data

The majority of PK data for LCS16 was provided by the pivotal Phase III LCS16 efficacy Study Protocol 91665/310442 (CSRs A52238 and PH-37274) and the Phase II Study Protocol 308901 (CSR A46796). The Phase III LCS16 efficacy study was a multicentre, open label, randomised, 2 arm parallel group trial which assessed the efficacy and safety of LCS12 and LCS 16 in healthy women in need of contraception for 3 years. The study also included an open label single arm extension phase of the LCS16 group for up to 5 years.

Comment: The pivotal Phase III LCS16 efficacy Study 91665/310442 comprises a 3 year phase (Study report A52238, evaluated in the previous Jaydess submission) and the extension phase up to 5 years (Study report PH-37274).

Study A46796 was a multicentre, open label, randomised, parallel group dose-finding study to investigate LCS12 (n = 239) and LCS16 (n = 245) compared to Mirena (n = 254) in healthy women seeking contraception for a maximum of 3 years.

PK evaluation included non-compartmental analyses for LNG and SHBG determined in a small subset of the study population with dense PK sampling, and population PK analyses to investigate serum LNG and SHBG concentrations in the whole study population and to determine in vivo release rates of LCS16. PK data from Study A46796 and the 3 year Study A52238 were evaluated in the previous Jaydess submission. PK data from the extension Study PH-37274 will be discussed in this report.

Table 1. Submitted pharmacokinetic studies.

PK topic	Subtopic	Study ID	Synopsis
PK in healthy adults	General PK, Single dose	A229 (oral LNG)[a]	Absolute bioavailability of levonorgestrel from Microlut and dose linearity of levonorgestrel pharmacokinetics in 18 healthy, young women.

PK topic	Subtopic	Study ID	Synopsis
		A10982 (Mirena)[a]	A multicentre, open label, non-randomised study of SH G 00650 a (levonorgestrel IUS) in parous women seeking contraception to evaluate its efficacy, safety, and PK profile when inserted for 12 months.
	Multi dose	Nil	
	Bioequivalence, Single dose[b]	Nil	
	Multi dose	Nil	
	Food effect	Nil	
PK in special populations	Target population, Single dose[c]	Study A46796[a]	Multicentre, open, randomised, dose finding Phase II study to investigate for a maximum of three years ultra low dose LNG contraceptive intrauterine systems (LCS) releasing in vitro 12 µg/24 h and 16 µg/24 h of LNG compared to Mirena in nulliparous and parous women in need of contraception.
		Study A52238[a]/ PH-37274	Multi-centre, open, randomised, study to assess the safety and efficacy of two doses (in vitro 12 µg/24 h and 16 µg/24 h) of the ultra low dose LNG contraceptive intrauterine systems (LCS) for a maximum of 3 years in women 18 to 35 years of age and an extension phase of the 16 µg/24 h group (LCS16 arm) up to 5 years.
		Study 91775[a]	Multi-centre, open label, single arm study to assess efficacy, safety, bleeding pattern and pharmacokinetics of the ultra low dose LNG intrauterine contraceptive system (LCS) for a maximum of 3 years in women 18 to 40 years of age.
	Multi-dose	Nil	
	Hepatic impairment	Nil	In vitro study provided (Study A02495[a])
	Renal impairment	Nil	
	Neonates, infants, children or adolescents	Study 14371	

PK topic	Subtopic	Study ID	Synopsis
	Elderly	Nil	
	Other special population	Nil	
Genetic/ gender related PK	Males versus females	N/A	
	Other genetic variable	Nil	
PK interactions		Nil	
Population PK analyses	Healthy subjects		
	Target population		
	Other		

a) Evaluated in the previous Jaydess submission; b) bioequivalence of different formulations; c) subjects who would be eligible to receive the drug if approved for the proposed indication.

4.2. Summary of pharmacokinetics

4.2.1. Physicochemical characteristics of the active substance

The sponsor states the following:

'The LCS16 IUS consists of a hormone elastomer reservoir mounted on a T-shaped polyethylene frame (T-body). The drug reservoir is composed of a mixture of 19.5 mg LNG and polydimethylsiloxane (PDMS). This reservoir is covered by a PDMS membrane which regulates the release of LNG. LNG is present in finely dispersed crystalline form in the core where it slowly dissolves into the surrounding matrix. The molecules reach the surface of the drug reservoir by dissolution in the polymer and random diffusion. The LCS16 formulation is very similar to LCS12 formulation. Except for some minor design adaptions between LCS12 and LCS16, the main difference in these formulations is the length of the drug reservoir resulting in different LNG release rates'.

4.2.2. Pharmacokinetics in healthy subjects

4.2.2.1. Absorption

Study PH-37274

The population PK model (discussed below in Section 4.2.2.2) was applied to serum LNG concentration and serum SHBG concentration data from the LCS16 treatment arm in Study PH-37274. Total and unbound LNG concentrations were estimated for all subjects (see Table 2 and Table 3 below). The total and unbound LNG concentrations decrease over time, although the variability remains relatively constant (geometric CV between 40.1 to 42.3% for total and 25.5 to 25.9% for unbound). Only a small fraction of total LNG is unbound (approximately 1.5%).

Table 2. Summary statistics of total LNG serum concentration estimated based on the population PK model for the complete LCS16 study population at pre-defined time points

Time after insertion	N	Geometric mean (ng/L)	95% CI	Geometric CV (%)
1 month	1253	152	149; 156	40.1
3 months	1223	142	139; 146	40.3
1 year	1109	115	113; 118	41.0
2 years	963	99.7	97.3; 102	41.2
3 years	774	91.3	88.8; 94.0	41.7
4 years	666	86.2	83.6; 88.9	42.3
4.5 years	624	84.5	81.9; 87.2	41.8
5 years	224	83.1	78.9; 87.5	41.1

Table 3. Summary statistics of unbound LNG serum concentration estimated based on the population PK model for the complete LCS16 study population at pre-defined time points

Time after insertion	N	Geometric mean (ng/L)	95% CI	Geometric CV (%)
1 month	1253	2.35	2.31; 2.38	25.8
3 months	1223	2.18	2.15; 2.21	25.7
1 year	1109	1.75	1.72; 1.77	25.6
2 years	963	1.49	1.47; 1.52	25.5
3 years	774	1.36	1.34; 1.38	25.6
4 years	666	1.28	1.26; 1.30	25.9
4.5 years	624	1.25	1.23; 1.28	25.6
5 years	224	1.23	1.19; 1.27	25.5

The effect of the covariates body weight and age were tested on the apparent clearance (CL/F) of LNG and the parameter for the SHBG serum concentration at baseline. A statistically significant influence was only found for body weight on CL/F. The CL/F increases linearly by 0.84% per kg body weight for the body weight range within this study (39 to 160 kg, median 65 kg with corresponding CL/F values of 188-432 L/h and 240 L/h respectively).

Comment: The clinical evaluator for the Jaydess submission reported an effect on body weight on the clearance parameter for data from the 3 year Study A52238. The clinical evaluator identified this as an important point given the small number of subjects with BMI > 30 kg/m^2. The sponsor is asked to comment on the clinical implications for women with BMI > 30 kg/m^2. See Clinical Questions below.

Non-compartmental PK analysis: The PK analysis set included 6 subjects from subset 3 of the FAS evaluated at 3 years. There were 3 subjects with valid LNG serum concentration values during the 5 year treatment period who were included in the non-compartmental evaluation after 5 years.

LNG concentration versus time: Following insertion of LCS16, mean C_{max} was 214 ng/L, reached after 4 days (median). Serum concentrations decline steadily until about 18 months after insertion to reach plateau like concentrations around 100 ng/L until 3 years after insertion. Serum concentrations decline slowly thereafter until about 74 ng/L. Over the whole treatment period the variability remained similar with a coefficient variation between approximately 20 and 30% for the 5 year treatment period (n = 3) and between approximately 40 to 60% for the 3 year treatment period (n = 6).

LNG mean PK parameters: The mean PK parameters are shown below in Table 4. Mean C_{max} (214 ng/L) was reached shortly after insertion (median t_{max} = 4.0 days). For the complete 5 year treatment, the mean systemic exposure ($AUC_{(0\text{-}tlast)}$) was 179010 ng d/L (CV 11.4%) and the average concentration (C_{av}) was 98.7 ng/L (CV 11.4%). Minimum concentrations (geometric mean 60.2 ng/L) were reached towards the end of the study after about 5 years (median t_{min}: 1788 days).

Table 4. Mean pharmacokinetic parameters of LNG observed after insertion of LCS16 (5 year period, n = 3)

PK Parameter	Unit	N	Geometric Mean (ng/L)	Min ; Max	Geometric CV (%)
AUC(0-t_{last})	ng·d/L	3	179010	164763 ; 203822	11.4
C_{max}	ng/L	3	214	163 ; 295	30.7
C_{av}	ng/L	3	98.7	89.9 ; 112	11.4
C_{min}	ng/L	3	60.2	50.9 ; 66.7	14.7
C_{last}	ng/L	3	64.0	50.9 ;80.1	23.0
			Median [range]		
t_{max}	d	3	4.0	3.0 ; 8.0	
t_{min}	d	3	1788	1650 ; 1819	
t_{last}	d	3	1819	1788 ; 1832	

Residual LNG content analysis: The residual LNG content was determined in the used LCS16 devices from the subjects who prematurely discontinued the study treatment (either during the first 3 years or during the extension phase), 345 selected subjects completing the 3 year treatment and 345 selected subjects completing the 5 year treatment. There was a steady decline in residual LNG content over time from a maximum 20.1 mg shortly after insertion and minimum 0.5 mg after 1864 days. The sponsor stated this very low minimum residual content was found in only one of the subjects at the end of the 5 year treatment period, with all other measured residual contents ≥ 2 mg. On average a geometric mean residual content of 3.6 mg was found at the end of the 5 year treatment period.

Silver ion PK analysis: Silver ion concentration in serum was measured during the first 3 treatment years from subset 3 before insertion and at Visit 2, Visit 6 and Visit 10, but not in the extension phase. The Delegate for the Jaydess submission stated: *'In A52238 a subset (n = 12) had serum silver concentrations determined prior to and during treatment; no increases were detected with all concentrations except one pre-dose measurement below LLOQ of the bioanalytical method, 1 μg/mL; this LLOQ is within the range measured in populations not exposed to occupational silver, 0.072 to 1.4 μg/mL'.*

4.2.2.2. Bioavailability

Absolute bioavailability

There was no short term bioavailability study conducted due to the long term use of LCS16. The sponsor states this is justified as LCS16 is a mainly locally acting product with low systemic concentrations of LNG in serum. Instead, a long term in vitro dissolution method that adequately describes the in vivo behaviour of LCS16 over the anticipated time of IUS use was developed. The long term in vitro release rate tests were conducted on LCS batches used in the Phase II and Phase III studies.

The initial in vitro release of LCS16 on day 2 after one day of dissolution was approximately 28 μg/day. The LNG release rates of LCS16 decline quickly to approximately 17 μg/day for the Day 19 to 25 sampling period, after which LNG in vitro release rates of LCS16 decline more slowly. At 6 months, the in vitro release rate of LNG from LCS16 is approximately 13 μg/day, declining to approximately 7 μg/day after 5 years.

The in vivo release rates were calculated based on ex vivo residual content and plasma concentration data from women who prematurely discontinued or completed the study. A population PK model, previously developed based on clinical and in vitro release data, and refined using data from the 3 year Study A52238, was used to determine in vivo release rates over 5 years. Using data provided from in vitro release rates, in vivo release rates were determined 24 days, 60 days, 1 year, 3 years, and 5 years after insertion. In addition, an average release rate over 5 years of use was calculated. The sponsor states the same approach was used for the calculation of the in vivo release rates for the approved LCS12 product.

Based on the population PK approach, the in vivo release rate of LCS16 was 17.5 µg/day at Day 25, declining to 9.79 µg/day at 1 year. At 3 years, the in vivo release rate was 7.89 µg/day, after which the release rate remained relatively consistent until the end of year 5 (7.44 µg/day). The average release rate over the entire period of LCS16 use was 8.99 µg/day.

Table 5. Model-based estimated *in vivo* release rates from LCS16 and LCS12

Time point	Days after insertion	LCS16 *In vivo* release rate (µg/day)	LCS12 *In vivo* release rate (µg/day)
Day 25	24	17.5	14.0
2 months	60	15.3	9.6
1 year	365	9.8	6.0
3 years	1095	7.9	5.4
5 years	1825	7.4	--
Mean over 3 years	0-1095	--	6.4
Mean over 5 years	0-1825	9.0	

Bioavailability data was provided in Study A229, which determined the absolute bioavailability of LNG following oral administration of Microlut (LNG). This study has been evaluated in the previous Jaydess submission.

Bioavailability relative to an oral solution or micronised suspension

See the AusPAR/Attachment 2 for the previous Jaydess submission.[4]

Bioequivalence of clinical trial and market formulations

See the AusPAR/Attachment 2 for the previous Jaydess submission.[4]

Bioequivalence of different dosage forms and strengths

See the AusPAR/Attachment 2 for the previous Jaydess submission.[4]

Bioequivalence to relevant registered products

See the AusPAR/Attachment 2 for the previous Jaydess submission.[4]

Influence of food

See the AusPAR/Attachment 2 for the previous Jaydess submission.[4]

Dose proportionality

See the AusPAR/Attachment 2 for the previous Jaydess submission.[4]

Bioavailability during multiple-dosing

See the AusPAR/Attachment 2 for the previous Jaydess submission.[4]

Effect of administration timing

See the AusPAR/Attachment 2 for the previous Jaydess submission.[4]

4.2.2.3. Distribution

Volume of distribution

See the AusPAR/Attachment 2 for the previous Jaydess submission.[4]

Plasma protein binding

During the first 3 months, SHBG concentrations decreased from 87.5 nmol/L at Day 1 to 60.2 nmol/L and remained relatively stable thereafter. The mean concentration time course is similar to the 6 subjects evaluated in the 3 year phase of the study. See the AusPAR/Attachment 2 for the previous Jaydess submission for results of Study A46796 and Study A52238.[4]

Erythrocyte distribution

See the AusPAR/Attachment 2 for the previous Jaydess submission.[4]

Tissue distribution

See the AusPAR/Attachment 2 for the previous Jaydess submission.[4]

4.2.2.4. Metabolism

Interconversion between enantiomers

See the AusPAR/Attachment 2 for the previous Jaydess submission.[4]

Sites of metabolism and mechanisms/enzyme systems involved

See the AusPAR/Attachment 2 for the previous Jaydess submission.[4]

Non-renal clearance

See the AusPAR/Attachment 2 for the previous Jaydess submission.[4]

Metabolites identified in humans: active and other

See the AusPAR/Attachment 2 for the previous Jaydess submission.[4]

Pharmacokinetics of metabolites

See the AusPAR/Attachment 2 for the previous Jaydess submission.[4]

Consequences of genetic polymorphism

See the AusPAR/Attachment 2 for the previous Jaydess submission.[4]

4.2.2.5. Excretion

Routes and mechanisms of excretion

See the AusPAR/Attachment 2 for the previous Jaydess submission.[4]

Mass balance studies

See the AusPAR/Attachment 2 for the previous Jaydess submission.[4]

Renal clearance

See the AusPAR/Attachment 2 for the previous Jaydess submission.[4]

Intra and inter individual variability of pharmacokinetics

See the AusPAR/Attachment 2 for the previous Jaydess submission.[4]

4.2.3. Pharmacokinetics in the target population

See Section 4.2.2. above.

4.2.4. Pharmacokinetics in special populations

4.2.4.1. Pharmacokinetics in subjects with impaired hepatic function

No data provided.

4.2.4.2. Pharmacokinetics in subjects with impaired renal function

No data provided.

4.2.4.3. Pharmacokinetics according to age

Study 14371 was a Phase III multicentre, single arm safety study of LCS12 in post-menarchal female adolescents aged under 18 years of age for 12 months. The study population included 304 subjects, mean age 16.2 years (range 12 to 18 years), 97.7% nulliparous. The PK of LNG was

determined by applying a population PK model based on data from Study A52238 and including a covariate effect of bodyweight on the LNG clearance (n = 283 subjects analysed). An effect of body weight on the clearance parameter was observed with LNG clearance increasing linearly by 1.5% per kg body weight range within this study (42 to 115 kg, median 60 kg with corresponding CL/F values of 148 to 426 L/h and 217 L/h respectively).

The mean total LNG serum concentration decreased from 145 ng/L at 1 month, to 90.9 ng/L at 6 months with a slower decline thereafter to 77.8 ng/L at 12 months after insertion (see Table 6, below). The predicted serum concentrations of LNG were slightly higher compared to adult concentration data from Study A52238 (see Table 7, below) however the sponsor states the ranges predicted for adolescents lie completely within the ranges predicted for adults. The higher mean is attributed to the covariate effect of body weight on LNG clearance, with lower clearance resulting in higher systemic exposure.

Table 6. Summary of total LNG and total unbound LNG serum concentrations estimated based on the population PK (Study 14371)

Total LNG serum concentration

Time after insertion (months)	N	Geometric mean (ng/L)	95% CI	Geometric CV (%)
1	268	145	141 ; 149	24.7
3	263	110	107 ; 113	25.2
6	258	90.9	88.2 ; 93.8	25.3
9	246	82.9	80.3 ; 85.5	25.2
12	220	77.8	75.4 ; 80.3	24.3

Total unbound serum concentration

Time after insertion (months)	N	Geometric mean (ng/L)	95% CI	Geometric CV (%)
1	268	2.21	2.16 ; 2.27	20.3
3	263	1.66	1.62 ; 1.70	20.2
6	258	1.36	1.33 ; 1.40	20.1
9	246	1.24	1.21 ; 1.27	20.1
12	220	1.16	1.13 ; 1.19	19.5

Table 7. Comparison of total and unbound LNG serum concentrations for adolescents (Study 14371) and adults (Study A52238) based on the population PK model

	Total LNG		Unbound LNG	
Time after insertion (months)	Geometric mean (ng/L) with 95% CI Adolescents	Geometric mean (ng/L) with 95% CI Adults	Geometric mean (ng/L) with 95% CI Adolescents	Geometric mean (ng/L) with 95% CI Adults
1	145 (141 ; 149)	131 (129 ; 133)	2.21 (2.16 ; 2.27)	1.98 (1.96 ; 2.01)
3	110 (107 ; 113)	99.8 (98.2 ; 101)	1.66 (1.62 ; 1.70)	1.49 (1.48 ; 1.51)
12	77.8 (75.4 ; 80.3)	71.0 (69.8 ; 72.2)	1.16 (1.13 ; 1.19)	1.05 (1.04 ; 1.07)

4.2.4.4. Pharmacokinetics in breastfeeding

See the AusPAR/Attachment 2 for the previous Jaydess submission.[4]

4.2.4.5. Pharmacokinetics in other special population/with other population characteristic/ethnic differences

Study 91775 was a multicentre, open label, single arm study assessing the PKs, efficacy and safety of LCS12 in Asian Pacific women aged 18 to 40 years (FAS = 925; 92.6% Asian ethnicity).

The pharmacokinetics were evaluated using a non-compartmental PK evaluation in a subset of 10 Chinese women with a dense sampling plasma profile. Following insertion of LCS12, geometric mean serum concentrations of LNG reached a maximum concentration of 138 ng/L within 3.5 days, with LNG concentrations decreasing slowly thereafter over 3 years. Serum concentrations decreased from about 85 to 65 ng/L between 6 and 36 months after LCS12 insertion.

In addition, a population PK analysis was performed based on the sparsely collected LNG plasma samples of the whole study population. The predicted values of the population PK analysis were similar to the measured values in the PK subgroup. The in vivo release rate of LCS12 was 14 µg/day at Day 25 declining to 6.0 µg/day at 1 year after insertion and remaining relatively stable until the end of Year 3.

Both the non-compartmental and population PK evaluations were compared to evaluations of mainly Caucasian subjects from Studies A46796 and A52238. Taking into consideration different study design, non-compartmental PK parameters for LNG were similar between the 2 populations. Lower mean SHBG concentrations were observed in Chinese women compared to Caucasian women; the sponsor comments this may be explained by oral hormonal product use and various time periods when hormonal product intake was stopped prior to study start (noting when compared to Study A46796 mean baseline values were slightly lower with ranges largely overlapping). Population PK analysis of LNG and SHBG serum concentration data showed the geometric means of the total and unbound LNG concentrations at 3 months, 1 year, 2 years and 3 years were slightly higher for Asian Pacific women compared to Caucasian women (see Table 8 below). The in vivo release rates from LCS12 in Asian Pacific women and Caucasian women were similar (see Table 9 below).

Table 8. Geometric mean values (95% CI) and geometric coefficient of variation [CV %] of estimated total and unbound LNG concentrations from Study PH-37275 (mainly Asian women) and on LCS12 data from Study A52238 (with mainly Caucasian women)

	Total LNG [ng/L]		Unbound LNG [ng/L]	
Time after insertion	Women from Asian-Pacific study	Caucasian women	Women from Asian-Pacific study	Caucasian women
3 months	104 (102;107) [36.0]	99.8 (98.2;101) [27.2]	1.52 (1.50;1.55) [21.9]	1.49 (1.48;1.51) [21.5]
1 year	79.1 (77.0;81.3) [36.7]	71.0 (69.8;72.2) [27.3]	1.14 (1.12;1.16) [21.8]	1.05 (1.04;1.07) [21.3]
2 years	70.4 (68.5;72.4) [36.2]	64.3 (63.1;65.5) [27.6]	1.01 (0.994;1.03) [21.4]	0.947 (0.933;0.961) [21.4]
3 years	65.5 (61.7;69.4) [37.3]	58.6 (56.5;60.8) [29.4]	0.947 (0.912;0.985) [23.8]	0.871 (0.847;0.896) [23.1]

Table 9. Comparison of model based estimated in vivo release rates from LCS12

Time point	Days after insertion	*In vivo* release rates (µg/day) Asian-Pacific	*In vivo* release rates (µg/day) Caucasian
Day 25	24	13.7	14.0
2 months	60	9.2	9.6
1 year	365	6.0	6.0
3 years	1095	5.5	5.4
Mean over 3 years	0-1095	6.5	6.4

4.2.5. Pharmacokinetic interactions

No new data submitted. The clinical evaluator the previous Jaydess submission stated the following:

'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'.

4.2.6. Clinical implications of in vitro findings

See the AusPAR/Attachment 2 for the previous Jaydess submission.[4]

4.3. Evaluator's overall conclusions on pharmacokinetics

The pharmacokinetic profile of LNG has been described in the previous submission for the lower strength product LCS12 (Jaydess). The current submission included additional PK data from the two clinical studies to support the longer term (5 year) use of LCS16.

Release of LNG occurs immediately after insertion of LCS16. The in vivo release rates calculated over the 5 year period demonstrate a reduction over the first 12 months, with rates remaining relatively stable thereafter to 5 years. The mean release rate over the 5 year period was 9.0 µg/day. By comparison, the mean release rate over the 3 year period for LCS12 was 6.4 µg/day.

As both LCS16 and LCS12 mainly act locally, the following comments from the clinical evaluator of the Jaydess submission are endorsed:

'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 were 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'.

Given the effect of bodyweight on LNG clearance, the clinical evaluator of Jaydess submission did raise the issue of use of LCS12 in obese women:

'On examining the pharmacometric work on clearance in the obese, 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'. See Section: Clinical Efficacy and Section: Clinical Questions, below.

5. Pharmacodynamics

5.1. Studies providing pharmacodynamic information

Pharmacodynamic information included effects on ovulation, cervical mucus, endometrium, serum oestradiol concentration. Data was provided in the Phase II Study A46796, and the Phase III LCS 16 efficacy study.

5.2. Summary of pharmacodynamics

5.2.1. Mechanism of action

The mechanism of action is mainly local progestogenic effects within the uterine cavity. These effects include down regulation of endometrial oestrogen and progesterone receptors resulting in an antiproliferative endometrium relatively insensitive to circulating oestradiol, thickening of

cervical mucus which impedes the passage of sperm, and inhibition of sperm motility and function.

5.2.2. Pharmacodynamic effects

5.2.2.1. Primary pharmacodynamic effects

Ovarian function

In both clinical studies, ovulation was assessed by serum progesterone (and serum oestradiol in Study A46796) measurements taken twice a week for six weeks in the second half of each year (LCS12 Years 1 to 3 and LCS16 Years 1 to 5) in subsets of 7 to 21 women per treatment group.

In Study A46796, the clinical evaluator for the previous Jaydess submission stated there was evidence of ovulation was observed in most women in all examinations in the LCS16 group (n = 15), except in the first year during which 2 women were anovulatory. For the LCS12 group (n = 21) evidence of ovulation was observed in all women at all examinations where an assessment was possible, and for the Mirena group (n = 17), there was a greater tendency for anovulation (4 women in the first year, 2 in the second and 1 in the third) (see the AusPAR/Attachment 2 for the previous Jaydess submission).[4]

In the Phase III LCS16 efficacy study, ovulation was based on serum progesterone values (threshold > 2.5 ng/mL). See the AusPAR/Attachment 2 for the previous Jaydess submission for the 3 year results.[4] In the subset of women treated with LCS16, evidence of ovulation was shown for 11 of 12 women in Year 1, 9 of 10 in Year 2, 7 of 7 in Year 3 and 1 of 1 in Year 4. There were no subjects left in the subset in Year 5. The same results were observed with a higher threshold of > 3.0 ng/mL.

Cervical function

The Delegate for the previous Jaydess submission noted low cervical scores, indicating thickening of cervical mucus, was observed for all treatments in both Study A46796 and the 3 year Study A52238. For the LCS16 group, there was one subject left in the subset in Year 4, with a low mean total cervical score reported.

Endometrial histology

For Study A46796 and the 3 year Study A52238, the Delegate for the previous Jaydess submission stated endometrial biopsies were taken on a yearly basis up to the end of the 3 year period in subsets of 30 per treatment arm in both studies. The Delegate reported *'a strong progestin effect and secretory endometrium was observed in the majority of cases indicating a high degree of endometrial suppression during treatment'*.

Endometrial histology was studied at Baseline and once a year in a subset of 29 women treated with LCS16 (15 in extension group and 14 in the 3 year group) in the Phase III LCS16 efficacy study. A reduction in oestrogen effect an increase in progesterone effect was observed during the first year of treatment and remained stable during the study period. At Baseline the endometrium was proliferative in 26 subjects and secretory in 2 subjects; by the end of study, the endometrium was secretory in all subjects whose endometrium could be classified (n = 10). A marked progesterone effect on the endometrium was observed at all time points with no abnormal changes reported.

Serum oestradiol concentration

The clinical evaluator for the previous Jaydess submission noted the variability in serum oestradiol concentrations (samples collected twice a week for 6 weeks per year) in Study A52238 (see the AusPAR/Attachment 2 for the previous Jaydess submission).[4] The Delegate noted the oestradiol values were stated to fall within the normal range for menstrual cycles (C_{av} values were between 98.8 and 126.6 pg/mL). For the LCS16 treatment arm, the mean average values also showed variability (range 94 pg/mL and 112 pg/mL) during the first

3 years, within the typical range for normal menstrual cycles. Oestradiol was measured for only 1 subject in Year 4, and no subjects in Year 5.

5.3. Evaluator's overall conclusions on pharmacodynamics

LCS16 acts primarily via local effects within the uterine cavity and cervix. The majority of data were provided in the 3 year Study A52238, with few subjects remaining within the subset for assessment during the extension phase. However, no change in pharmacodynamic effect would be expected in the extension phase given the release rates and serum concentrations of LNG over time as discussed above. Evidence of ovulation was present in almost all subjects during the 3 year study suggesting serum LNG concentrations were not sufficient to exert an inhibitory effect on ovulation. There was variability in circulating oestradiol levels, although values remained within the range for normal menstrual cycles. A strong progestogenic effect on the endometrium and cervix was observed indicating a high degree of endometrial suppression and thickening of cervical mucus respectively.

6. Clinical efficacy

6.1. Studies providing evaluable efficacy data

The two clinical efficacy studies providing evaluable data were the Phase II Study Protocol 308901 (CSR A46796) and the pivotal Phase III LCS16 efficacy Study Protocol 91665/310442 (CSRs A52238 and PH-37274). Study A46796 and the 3 year Study A52238 have been evaluated previously in the Jaydess submission; this report will cross reference the Clinical Evaluation Report and the Delegate's Overview where appropriate [details of which are available via the AusPAR/Attachment 2 for the previous Jaydess submission].[4] The submission includes new data from the 5 year Study PH-37274.

6.2. Pivotal or main efficacy studies

6.2.1. Study 91665/310442

6.2.1.1. Study design, objectives, locations and dates

Study 91665/310442 was a multicentre, open label, randomised, 2 arm parallel group study to assess the safety and contraceptive efficacy of two doses (LCS12 (in vitro 12 µg/24 h) and LCS16 (in vitro 16 µg/24 h)) of low dose levonorgestrel contraceptive intrauterine systems (LCS) in healthy women aged 18 to 35 years for a maximum of 3 years. The study also included an open label single arm extension phase of the LCS16 group up to 5 years, which is the focus of this report.

The study population comprised 2884 healthy nulliparous and parous women aged 18 to 35 years in need of contraception. Subjects were randomised in a 1:1 ratio to either the LCS12 (n = 1432) or LCS16 (n = 1452) treatment arms. At the end of the three years, there were 707 subjects in the LCS16 treatment arm who continued in to the single-arm extension study. There was no control group.

The primary efficacy variable was pregnancy rate, calculated as the Pearl Index (PI; number of pregnancies per 100 woman-years) and life-table analysis. Secondary variables included bleeding pattern, return to fertility and user satisfaction. After the baseline visit, study visits were conducted at 3 monthly intervals for the first year, then 6 monthly until the Year 3 end of study visit. For the LCS16 single arm extension study, there were 4 additional study visits at 6 monthly intervals from 36 to 60 months. Serum pregnancy testing was performed at screening, and interim visits as needed. Urine pregnancy testing was performed at Baseline, Visit 10 (36 months), Visit 12 (48 months) and Visit 14 (60 months).

The study was conducted at 138 sites (109 sites during the extension phase) across Europe, North America and South America from 20 August 2007 to 7 June 2013. There were 6 amendments to the original study protocol.

6.2.1.2. Inclusion and exclusion criteria

Inclusion criteria were women aged 18 to 35 years inclusive seeking contraception with regular menstrual cycles and in otherwise good health.

Exclusion criteria included delivery or abortion within 6 weeks, history of ectopic pregnancy, PID, clinically significant ovarian cysts, congenital or acquired uterine anomalies, any distortion of the uterine cavity likely to cause problems (in the opinion of the investigator) during insertion, retention or removal of the LCS, concomitant use of other sex hormone containing preparations, and use of any long-acting injectable sex hormone preparations within 12 months prior to start of study medication.

6.2.1.3. Study treatments

Subjects were randomised in a 1:1 ratio to either the LCS12 (n = 1432) or LCS16 (n = 1452) treatment arms.

6.2.1.4. Efficacy variables and outcomes

The primary efficacy variable was the occurrence of pregnancy, determined by the Pearl Index (number of pregnancies per 100 woman-years). As a secondary analysis, the cumulative failure rate (that is, the probability of getting pregnant) was calculated using the Kaplan-Meier method.

Secondary efficacy variables were:

- Treatment compliance:
  - determined by location of IUS by ultrasound examination, performed at each study visit. Compliance was met if the IUS location was in the fundal position (in situ) or displaced but still completely within the uterine cavity (displaced intrauterine). The presence of the removal threads was also checked at each visit.
- Uterine bleeding pattern:
  - bleeding indices were based on subject diary data. A reference period of 90 days was to be used to present bleeding events, with 30 day reference periods used for the first year. The proportion of women with amenorrhea, prolonged, frequent, infrequent and irregular bleeding was calculated according to WHO criteria.
- User satisfaction:
  - based on the user satisfaction questionnaire.
- Return to fertility:
  - all women were contacted at 3 months after the end of study treatment to record any pregnancies occurring after LCS removal. Those women who discontinued treatment due to desire for pregnancy were to contact the study site if they fell pregnant within 3 months after the end of study visit, otherwise were contacted at 12 months to assess post-treatment pregnancy outcomes.

6.2.1.5. Randomisation and blinding methods

Treatment was assigned using a computerised randomisation list prepared for each study site. Subjects were randomised in a 1:1 ratio to either treatment arm. Subjects were blinded to treatment allocation. For those subjects in the LCS16 treatment group, the study treatment was revealed at Visit 9 (30 months); these subjects were informed they could continue the study treatment for up to 5 years.

The study was open, although all evaluators of efficacy or safety outcomes, except for investigators and study nurses, were to remain blinded to treatment as far as possible.

6.2.1.6. Analysis populations

All safety and efficacy assessments were conducted on the full analysis set (FAS), which included all randomised subjects who received treatment (at least one insertion attempt), using the treatment actually received.

In total, 2871 (99.5%) women had successful insertions:

- LCS12: 1426 women (n = 1380 successful at the first attempt and n = 46 successful at the second attempt).
- LCS16: 1445 women (n = 1390 successful at the first attempt and n = 55 successful at the second attempt).

All women with an unsuccessful insertion were included in the FAS (n = 13; LCS12 = 6 and LSC16 = 7). The FAS comprised 2884 subjects for the 3 year study and 1452 subjects for the single arm LCS16 extension phase.

Additional variables (ovarian and cervical function, endometrial histology, pharmacokinetics and bone mineral density) were studied in 4 subsets in pre-selected centres. Those subjects participating in the extension phase in the LCS16 treatment arm were to continue in their respective subset.

6.2.1.7. Sample size

Assuming a true Pearl Index of 1.0, annual drop-out rate of 15%, and reduction in exposure time by an additional 2% (due to the use of an additional concomitant contraceptive method) the sponsor states there should be 1410 subjects per treatment group to end with sufficient exposure time in the third year of treatment. This sample size would be sufficient for the extension phase of the study; assuming a yearly drop-out rate of 20% and that only 50% of the women completing the 3 years of LCS16 treatment will continue in the extension phase, the number of women who will complete 5 years of LCS16 treatment will still be approximately 237. The sponsor states this is in accordance with the EMA guideline Guideline on clinical investigation of steroid contraceptives in women (EMA/CPMP/EWP/519/ Rev1, July 2005) which requires that the number of women completing the claimed duration of use should be at least 200 for long-acting products.

There were a total of 2884 patients randomised to either of the treatment groups (LCS12 = 1432 and LCS16 = 1452). There were 707 subjects in the LCS16 treatment arm who continued in to the extension study.

6.2.1.8. Statistical methods

The main statistical analysis was to be conducted after all patients had completed the originally planned 3 years of treatment. The statistical analysis was to be based on all data up to 3 years of treatment for each subject. The LCS16 treatment arm was to be analysed again after 5 years of treatment. The primary efficacy variable was the occurrence of pregnancy, calculated as the Pearl Index with 2-sided 95% confidence intervals. Several different Pearl Indices were calculated, as the sponsor states the usual assumption for the calculation of the Pearl Index is a constant hazard for the event of becoming pregnant over time and this could not necessarily be assumed for the experimental treatments of this study.

For the first three years the following Pearl Indices were calculated:

- First year Pearl Index: Pearl Index obtained in the first year of treatment (number of pregnancies that occurred during the first year of treatment divided by time the women were at risk of getting pregnant in the first year of treatment).

- Second year Pearl Index: Pearl Index obtained in the second year of treatment (number of pregnancies that occurred during the second year of treatment divided by time the women were at risk of getting pregnant in the second year of treatment).
- Third year Pearl Index: Pearl Index obtained in the third year of treatment (number of pregnancies that occurred during the third year of treatment divided by time the women were at risk of getting pregnant in the third year of treatment).
- 2 year Pearl Index: Pearl Index obtained in the first 2 years of treatment (number of pregnancies that occurred during the first 2 years of treatment divided by time the women were at risk of getting pregnant in the first two years of treatment).
- 3 year Pearl Index: Pearl Index obtained in the first 3 years of treatment (number of pregnancies that occurred during the first 3 years of treatment divided by time the women were at risk of getting pregnant in the first three years of treatment).
- Overall Pearl Index: Pearl Index obtained during the whole study, that is, the number of pregnancies that occurred during treatment divided by the time the women were at risk of getting pregnant.

For the extended LCS16 treatment arm the following Pearl Indices were calculated:

- Fourth year Pearl Index: Pearl Index obtained in the fourth year of treatment (number of pregnancies that occurred during the fourth year of treatment divided by time the women were at risk of getting pregnant in the fourth year of treatment).
- Fifth year Pearl Index: Pearl Index obtained in the fifth year of treatment (number of pregnancies that occurred during the fifth year of treatment divided by time the women were at risk of getting pregnant in the fifth year of treatment).
- 4 year Pearl Index: Pearl Index obtained in the first four years of treatment (number of pregnancies that occurred during the first four years of treatment divided by time the women were at risk of getting pregnant in the first four years of treatment).
- 5 year Pearl Index: Pearl Index obtained in the first five years of treatment (number of pregnancies that occurred during the first five years of treatment divided by time the women were at risk of getting pregnant in the first five years of treatment).

The Pearl Index was calculated as: Pearl Index = x/E, where x = number of pregnancies, and E = exposure in 100 woman-years (one woman-year is 365 days of treatment exposure).

The Pearl Indices for the 3 years of treatment (that is the 3 year Pearl Index) and for the first year of treatment (that is, the first year Pearl Index) were the primary criteria to assess contraceptive reliability during the 3 year two arm phase of the study.

The primary outcome for the extension phase of the study was the overall Pearl Index (Pearl Index obtained during the whole study, that is, the number of pregnancies that occurred during treatment divided by the time the women were at risk of getting pregnant).

Unadjusted and adjusted Pearl Indices were calculated:

For the unadjusted Pearl Index the exposure time until removal or total expulsion was to be used. Pregnancies that occurred after partial expulsion, but before LCS removal were to count for the unadjusted Pearl Indices.

For the adjusted Pearl Indices, only the exposure time until the IUD was last known to be in situ or displaced within the uterine cavity was to be considered. Pregnancies that occurred when the LCS was definitely not in-situ or displaced in the intrauterine cavity were not to count for any adjusted Pearl Index.

Pregnancies that occurred after the LCS had been removed or after an expulsion had been noticed were not to count for any Pearl Index.

The relevant exposure time was the total exposure time excluding the period (in terms of calendar months) in which concomitant contraception was used (for example, condoms to prevent STD, or any excluded hormonal preparations). All subjects were instructed to use condoms for contraception starting at least 7 days before LCS removal, unless the removal was to take place during the first 7 days of the menses. Therefore, the week before removal of the LCS was to be subtracted from the exposure for all subjects. Missing data were to be considered as no concomitant use of a contraceptive method.

As a secondary analysis, the cumulative failure rate (that is, the probability of getting pregnant) was calculated using the Kaplan-Meier method.

Comment: Over 98% of subjects treated with LCS16 were sexually active after their previous visit between Baseline and the end of extension (except at Month 36 where the incidence was 96.6%). During treatment Years 1 to 5, most women (≥ 79.5%) did not use backup contraception at all (for example, condoms to prevent STD); in each year, less than 1.0% of women used backup contraception for 6 months or more. In Year 5, 12.9% of women used back-up contraception for up to one month; this corresponds to the requirement discussed above regarding condom use before LCS removal. The sponsor states therefore the final week of treatment for all subjects was subtracted from the total exposure time (as well as any exposure time for individual women during which backup contraception was used).

6.2.1.9. Participant flow

There were 3661 women screened, and 2885 randomised. The most common reasons for screen failure (n = 776) were not meeting inclusion exclusion criteria (n = 404) and withdrawal of consent (n = 164).

There were 1196 subjects (41.5%) in total who discontinued the study prematurely over the first three years (LCS12 = 613 (42.8%) and LCS16 = 583 (40.1%)):

- 511 (17.7%) subjects during the first year (LCS12 = 266 and LCS16 = 245).
- 397 (16.7%) subjects in the second year (LCS12 = 203 and LCS16 = 194).
- 285 (14.4%) subjects in the third year (LCS12 = 144 and LCS16 = 142).

The most common reasons for premature discontinuation in both groups was adverse event (LCS12 = 313/613 (51.1%) and LCS16 = 278/583 (47.7%)), and 'other' (LCS12 = 186/613 (30.3%) and LCS16 = 186/583 (31.9%)). The main reasons for 'other' were wish for pregnancy, no further need for contraception, and not able to attend visits. The clinical evaluator of the original submission commented *'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'* (see also the AusPAR/Attachment 2 for the previous Jaydess submission).[4]

Of the 870 subjects completing the 3 year treatment in the LCS16 treatment group, 707 continued in the LCS16 extension phase, with 550 (77.8%) of these subjects completing the study at Year 5, and 157 (22.2%) subjects discontinuing prematurely during the extension phase of the study. The most common reason for discontinuation during the extension phase was 'other' (n = 100 (14.1%); same reasons as during first 3 years) and adverse event (n = 36 (5.1%)). See Table 10, below.

Table 10. Study PH-37274 Number of premature discontinuations after randomisation and their reasons (all randomised subjects)

No of subjects	LCS16 First 3 years N = 1453 n (%)	LCS16 Extension (after year 3) N = 707 n (%)
Study medication administered	1452 (>99.9%)	707 (100.0%)
Completed study phase (3 years or Extension)	163 (11.2%) [a]	550 (77.8%)
Prematurely discontinued	583 (40.1%)	157 (22.2%)
Reason for discontinuation		
Withdrawal of consent	31 (2.1%)	3 (0.4%)
Protocol deviation	16 (1.1%)	2 (0.3%)
Adverse event	278 (19.1%)	36 (5.1%)
Death	1 (<0.1%)	1 (0.1%)
Lost to follow-up	61 (4.2%)	12 (1.7%)
Pregnancy	10 (0.7%)	3 (0.4%)
Other	186 (12.8%)	100 (14.1%)

N = total number of subjects, n = number of subjects with event
a: These 163 subjects completed the 3 year phase but did not enter the extension phase (i.e. chose to end participation at 3 years)

6.2.1.10. Major protocol violations/deviations

Protocol deviations assessed as major were reported for 61 subjects (LCS12 = 39 (2.7%) and LCS16 = 22 (1.5%)) during the 3 year study. Almost all major protocol deviations were due to excluded concomitant medication use, and there were no major protocol deviations which lead to exclusion from the analyses. See the AusPAR/Attachment 2 for the previous Jaydess submission).[4]

For those subjects treated with LSC16, protocol deviations assessed as major were reported for 26 subjects (1.8%; n = 17 no extension group and n = 9 in extension group). The major protocol deviations were all due to excluded concomitant treatment use and did not lead to exclusion from the analyses.

6.2.1.11. Baseline data

In Study A52238, the majority of subjects were Caucasian (80.0%), with a mean age of 27.1 years (40% aged ≤ 25 years) and mean BMI 25.3 kg/m^2; 39.2% were nulliparous. The clinical evaluator of the previous Jaydess submission stated the demographics were similar between the two groups and considered study population representative of the relevant target population. See Table 11 below.

Table 11. Study A52238 Summary of demographic and baseline characteristics (FAS)

Variable	LCS12 N = 1432 (100%)	LCS16 N = 1452 (100%)	Total N = 2884 (100%)
Mean age (years [range])	27.2 [18-35]	27.1 [18-35]	27.1 [18-35]
Ethnic group (n [%])			
Caucasian	1142 (79.7%)	1164 (80.2%)	2306 (80.0%)
Mean weight (kg)	68.7	68.7	68.7
Mean height (m)	1.647	1.647	1.647
Mean body mass index (kg/m^2)	25.32	25.32	25.32
Currently sexually active	1416 (98.9%)	1435 (98.8%)	2851 (98.9%)
Current smokers	334 (23.3%)	360 (24.8%)	694 (24.1%)
Mean number of cigarettes smoked per day	7.8	7.9	7.9
Alcohol consumption			
seldom/occasional	1067 (74.5%)	1079 (74.3%)	2146 (74.4%)
Education level			
some secondary	970 (96.3%)	996 (96.7%)	1966 (96.5%)

The subjects in the LCS16 extension group were similar to subjects in the LCS16 no extension group in regard to demographics, baseline characteristics and gynaecological history.

Of the 707 subjects continuing the 5 year extension, 82.5% were Caucasian, mean age 27.6 years (35.9% ≤ 25 years, 64.1 % > 25 ≤ 35 years), mean BMI 25.1 kg/m^2. There were 37.1% of subjects who were nulliparous. See Table 12 and 13 below.

Table 12. Study PH-37274 Demographics and baseline characteristics, all subjects treated with LCS16 (FAS)

Variable	No-extension group N = 745 (100%) n (%)	Extension group (FAS) N = 707 (100%) n (%)	Total N = 1452 (100%) n (%)
Age category			
≤ 25 years	310 (41.6%)	254 (35.9%)	564 (38.8%)
> 25 years ≤ 35 years	435 (58.4%)	453 (64.1%)	888 (61.2%)
Age (years)			
Mean (SD)	26.6 (4.7)	27.6 (5.0)	27.1 (4.9)
Min, Max	18, 35	18, 35	18, 35
Race			
Caucasian	581 (78.0%)	583 (82.5%)	1164 (80.2%)
Black	55 (7.4%)	19 (2.7%)	74 (5.1%)
Hispanic	81 (10.9%)	78 (11.0%)	159 (11.0%)
Asian	9 (1.2%)	8 (1.1%)	17 (1.2%)
Other [a]	19 (2.6%)	19 (2.7%)	38 (2.6%)
Weight (kg)			
Mean (SD)	69.7 (16.2)	67.6 (14.6)	68.7 (15.5)
Min, Max	39, 173	38, 153	38, 173
Height (cm)			
Mean (SD)	165.1 (7.0)	164.2 (7.2)	164.7 (7.1)
Min, Max	142, 186	124, 188	124, 188
Body mass index (kg/m^2)			
Mean (SD)	25.54 (5.66)	25.09 (5.30)	25.32 (5.49)
Min, Max	15.2, 56.5	15.2, 57.6	15.2, 57.6
Currently sexually active			
No	12 (1.6%)	5 (0.7%)	17 (1.2%)
Yes	733 (98.4%)	702 (99.3%)	1435 (98.8%)
Current smokers			
No	555 (74.5%)	537 (76.0%)	1092 (75.2%)
Yes	190 (25.5%)	170 (24.0%)	360 (24.8%)
Number of cigarettes per day [b]			
Mean (SD)	7.8 (5.8)	8.0 (6.2)	7.9 (5.9)
Min, Max	0, 25	0, 20	0, 25
Alcohol consumption [c]			
Never	157 (21.1%)	160 (22.6%)	317 (21.8%)
Seldom	253 (34.0%)	250 (35.4%)	503 (34.6%)
Occasionally	304 (40.8%)	272 (38.5%)	576 (39.7%)
Regularly	31 (4.2%)	25 (3.5%)	56 (3.9%)
Education level [d]			
Some elementary education	7 (0.9%)	27 (3.8%)	34 (2.3%)
Some secondary education	88 (11.8%)	227 (32.1%)	315 (21.7%)
Some college or university education	285 (38.3%)	396 (56.0%)	681 (46.9%)
Information missing	365 (49.0%)	57 (8.1%)	422 (29.1%)

Table 13. Gynaecological history, all subjects treated with LCS16 (FAS)

	No-extension group N = 745 n (%)	Extension group N = 707 (100%) n (%)	Total N=1452 n (%)
Number of births			
0	312 (41.9%)	262 (37.1%)	574 (39.5%)
1	186 (25.0%)	147 (20.8%)	333 (22.9%)
2	193 (25.9%)	214 (30.3%)	407 (28.0%)
3	44 (5.9%)	69 (9.8%)	113 (7.8%)
Number of vaginal deliveries			
0	395 (53.0%)	348 (49.2%)	743 (51.2%)
1	154 (20.7%)	121 (17.1%)	275 (18.9%)
2	157 (21.1%)	171 (24.2%)	328 (22.6%)
3	30 (4.0%)	57 (8.1%)	87 (6.0%)
Number of abortions			
0	534 (71.7%)	520 (73.6%)	1054 (72.6%)
1	148 (19.9%)	129 (18.2%)	277 (19.1%)
2	45 (6.0%)	42 (5.9%)	87 (6.0%)
3	12 (1.6%)	9 (1.3%)	21 (1.4%)
Number of cesarean sections			
0	636 (85.4%)	580 (82.0%)	1216 (83.7%)
1	75 (10.1%)	85 (12.0%)	160 (11.0%)
2	30 (4.0%)	34 (4.8%)	64 (4.4%)
3	4 (0.5%)	7 (1.0%)	11 (0.8%)
Number of ectopic pregnancies [a]			
0	744 (99.9%)	705 (99.7%)	1449 (99.8%)
Age at menarche			
Mean (SD)	12.6 (1.5)	12.6 (1.4)	12.6 (1.4)
Min, Max	9, 18	9, 18	9, 18

6.2.1.1. Results for the primary efficacy outcome

3 year data (Study A52238)

There were a total of 20 pregnancies over the 3 year study (n = 10 in each group). The relevant 3 year exposure for the PI was similar in the two treatment groups: 3058.62 WY and 3211.36 WY for the LCS12 and LCS16 groups respectively.

The unadjusted Pearl Index for the first year was 0.41 (95% CI: 0.13, 0.96) for the LCS12 group and 0.16 (95% CI: 0.02, 0.58) for the LCS16 group. The 3 year unadjusted Pearl Index was 0.33 (95% CI: 0.16, 0.60) for LCS12, and 0.31 (95% CI: 0.15, 0.57) for LCS16.

The cumulative failure rate over 3 years for all women (18 to 35 years) was 0.009 (95% CI: 0.005, 0.017) in the LCS12 group and 0.010 (95% CI: 0.005, 0.018) in the LCS16 group. See also the AusPAR/Attachment 2 for the previous Jaydess submission.[4]

5 year data (Study PH-37274)

There were a total of 13 pregnancies observed on LCS16 treatment (n = 2 during the first year, n = 4 during the second year, n = 4 during the third year, n = 1 during the fourth year and n = 2 during the fifth year). Of the 13 pregnancies, n = 8 were ectopic/suspected ectopic, n = 2 spontaneous abortion, n = 1 missed abortion and n = 2 were normal pregnancies carried to term.

The relevant exposure in the 5 year study was 4434.53 WY. Due to decreasing subject numbers, the highest relevant unadjusted exposure by single year was seen during the first year (1252.43 WY of exposure), followed by the second year (1066.87 WY), third year (897.75 WY), fourth year (659.17 WY) and fifth year (558.30 WY) respectively.

The primary efficacy endpoint was the overall Pearl Index, which was 0.29 (95% CI: 0.16, 0.50), shown below in Table 14.

Table 14. Unadjusted Pearl Indices: All subjects with treated with LCS16 (FAS)

Time	Subjects N	Pregnancies n	Total exposure WY	Relevant exposure WY	Pearl index	Lower; Upper 95% CI
Overall	1452	13	4611.99	4437.31	**0.29**	0.16; 0.50
Year 1	1452	2	1316.41	1252.43	**0.16**	0.02; 0.58
Year 2	1206	4	1105.32	1066.87	**0.37**	0.10; 0.96
Year 3	1010	4	926.28	897.75	**0.45**	0.12; 1.14
Year 4	773	1	677.18	659.17	**0.15**	0.00; 0.85
Year 5	636	2	581.53	558.30	**0.36**	0.04; 1.29
2 years	1452	6	2421.73	2319.30	**0.26**	0.09; 0.56
3 years	1452	10	3348.01	3217.05	**0.31**	0.15; 0.57
4 years	1452	11	4025.18	3876.22	**0.28**	0.14; 0.51
5 years	1452	13	4606.71	4434.53	**0.29**	0.16; 0.50

CI = confidence interval; FAS = full analysis set; N = number of subjects; n = number of pregnancies; WY = women years (1WY = 365 days)
Note: the relevant exposure was calculated from the total exposure minus the time in which backup contraception was used or sex hormones were taken for other reasons

The Year 4 and Year 5 Pearl Indices were 0.15 (95% CI: 0.00, 0.85) and 0.36 (95% CI: 0.04, 1.29) respectively. The highest Pearl Index was 0.45 (95% CI: 0.12, 1.14) seen at Year 3, with no trend regarding pregnancy pattern observed over time. All Pearl Indices met the EMA guidance efficacy requirement that the difference between the point estimate for the Pearl Index and the upper limit of the 2-sided 95% CI should not exceed 1. Similar results were observed for the adjusted Pearl Indices as there were no pregnancies excluded from the analysis (see Table 15 below).

Table 15. Study PH-37274 Contraceptive efficacy (FAS, LCS16 treated subjects)

Pearl Index	Time	Number of subjects	Total exposure [WY]	Excluded exposure [WY]	Relevant exposure [WY]	Number of pregnancies	Pearl index	Lower 95% CIL	Upper 95% CIL
Unadj.	Overall	1452	4611.99	174.68	4437.31	13	0.29	0.16	0.50
	Year 1	1452	1316.41	63.98	1252.43	2	0.16	0.02	0.58
	Year 2	1206	1105.32	38.45	1066.87	4	0.37	0.10	0.96
	Year 3	1010	926.28	28.53	897.75	4	0.45	0.12	1.14
	Year 4	773	677.18	18.01	659.17	1	0.15	0.00	0.85
	Year 5	636	581.53	23.22	558.30	2	0.36	0.04	1.29
	2 years	1452	2421.73	102.42	2319.30	6	0.26	0.09	0.56
	3 years	1452	3348.01	130.95	3217.05	10	0.31	0.15	0.57
	4 years	1452	4025.18	148.96	3876.22	11	0.28	0.14	0.51
	5 years	1452	4606.71	172.18	4434.53	13	0.29	0.16	0.50
Adj.	Overall	1452	4570.60	171.46	4399.13	13	0.30	0.16	0.51
	Year 1	1452	1300.80	62.58	1238.22	2	0.16	0.02	0.58
	Year 2	1198	1095.61	37.87	1057.74	4	0.38	0.10	0.97
	Year 3	1000	919.49	28.20	891.29	4	0.45	0.12	1.15
	Year 4	765	672.79	17.81	654.98	1	0.15	0.00	0.85
	Year 5	633	577.53	22.81	554.73	2	0.36	0.04	1.30
	2 years	1452	2396.41	100.45	2295.96	6	0.26	0.10	0.57
	3 years	1452	3315.90	128.65	3187.24	10	0.31	0.15	0.58
	4 years	1452	3988.69	146.46	3842.23	11	0.29	0.14	0.51
	5 years	1452	4566.22	169.27	4396.96	13	0.30	0.16	0.51

The Kaplan-Meier estimate of the cumulative failure rate (unadjusted) over 5 years was 1.4 %. The cumulative failure rate over 3 years reported for subjects in the LCS16 treatment arm was 1.0%. See Table 16 below.

Table 16. Study PH-37274 Cumulative (5 year) failure rate by subgroup analysis (All LCS16 treated subjects, FAS)

	N Women / n pregnancies	Relevant exposure time (WY)	Cumulative failure rate (%)	Lower; Upper 95% CI
Cumulative 5-year failure rate				
All women	1452 / 13	4434.53	**1.445**	0.823; 2.531
By Parity				
Nulliparous	574 / 4	1636.24	**1.228**	0.454; 3.302
Parous	878 / 9	2798.28	**1.553**	0.789; 3.047
By Age				
18-25 years	564 / 3	1628.02	**0.910**	0.280; 2.933
>25-35 years	888 / 10	2806.51	**1.752**	0.927; 3.298
By BMI				
<30 kg/m²	1198 / 9	3701.88	**1.293**	0.659; 2.528
≥30 kg/m²	250 / 4	720.57	**2.153**	0.808; 5.668

Subgroup analysis: parity, age and BMI

Subgroup analysis by parity, age and BMI are shown below in Table 17. Of the 13 reported pregnancies, 9 occurred in the 878 parous subjects and 4 occurred in the 574 nulliparous subjects. Ten pregnancies occurred in the > 25 to 35 year age group, and 3 pregnancies in the 18 to 25 years age group. The 5 year unadjusted Pearl Index was numerically higher in the parous versus nulliparous subgroup, and the > 25 to 35 year age group versus the 18 to 25 years age group, although note is made of the overlapping confidence intervals.

Regarding BMI subgroup analysis, the number of subjects in the ≥ 30 kg/m² subgroup was small (n = 250 versus 1198 in the < 30 kg/m² subgroup), resulting in low total exposure compared to subjects in the < 30 kg/m² subgroup. There is a numerical difference in the Pearl Index between the two subgroups; 0.24 (95% CI: 0.11, 0.46) versus 0.56 (95% CI: 0.15, 1.42) for the < 30 kg/m² and ≥ 30 kg/m² subgroups respectively.

Table 17. Cumulative (5 year) analysis of Pearl Index by subgroup (All subjects treated with LCS16, FAS)

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

BMI = Body mass index; CI = confidence interval; FAS = full analysis set; N = number of subjects; PI = Pearl index; WY = women years.

Cumulative failure rate stratified by parity, age and BMI is shown in Table 16, above. The 5 year cumulative failure rate was similar for parous and nulliparous subjects (1.2% versus 1.6%), but higher for the > 25 to 35 years age group versus the 18 to 25 year age group (1.8% versus 0.9%), and the ≥ 30 kg/m² subgroup versus the < 30 kg/m² subgroup (2.2% versus 1.3%).

Subgroup analysis: ectopic pregnancy

Of the 13 pregnancies, 8 were ectopic (documented or suspected) (n = 2 occurred during the first year, n = 3 during the second year, n = 2 during the third year and n = 1 during the fourth year). The unadjusted 5 year Pearl Index for ectopic pregnancies was 0.18 (95% CI: 0.08, 0.36) and the yearly unadjusted Pearl Indices for ectopic pregnancies were equal to or below 0.28. Similar results were observed for the adjusted Pearl Indices. There was no evidence of a relevant difference among the subgroups was seen with regard to ectopic pregnancy rate. The 5 year cumulative failure rate for ectopic pregnancy was 0.8% (95% CI: 0.39, 1.62).

6.2.1.2. Results for other efficacy outcomes

Treatment compliance

3 year data (Study A52238): There were 2871 of 2990 subjects with successful insertions (96.0%; LCS12 = 1426 and LCS16 = 1445), the majority of which were successful at the first attempt (n = 2770 (96.0%); n = 101 successful at the second attempt). Compliance was consistently > 99% up to Month 30 and > 92% at the end of study visit (Month 36). The clinical evaluator of the original Jaydess submission commented this may have been explained by the way patients who had had their IUS removed or expelled were counted in the final visit.

5 year data (Study PH-37274): There were 1445 of 1452 randomised subjects with successful insertions (n = 1390 successful at the first attempt and n = 55 successful at the second attempt). Treatment compliance was over 99% up to Month 30, 95.1% at Month 36 (end of 3 year study) and again over 99% until the end of the extension when the compliance was 97.7%. The lower compliance at Month 36/EOS and extension EOS was due to premature discontinuations from expulsions and IUS removed prior to ultrasound. There was no difference in compliance between parous and nulliparous subjects at any visits, although for those subjects not continuing into the extension phase (n = 745), there were more LCSs displaced in the cervical canal in parous subjects (5.1%) versus nulliparous subjects (1.5%) at Month 36.

Bleeding profile

3 year data (Study A52238): For both treatment groups, there was an increase in the number of subjects with amenorrhoea, infrequent bleeding and normal bleeding, and a reduction in the

number of subjects with frequent, irregular and prolonged bleeding. See also the AusPAR/Attachment 2 for the previous Jaydess submission).[4]

5 year data (Study PH-37274): Vaginal bleeding data for LCS16 is provided in 90 day reference periods; there are 20 reference periods for the extension group, and 12 reference periods for the no extension group.

Bleeding patterns in days:

- the mean number of bleeding/spotting days decreased from 39.7 days in reference period one to 9.3 days in reference period 20, with the greatest reduction in mean number of bleeding days occurring between the first and second reference periods (39.7 to 21.1 days in reference period 2), after which a gradual decrease in mean bleeding/spotting days was observed.
- a similar trend was observed for the mean number of bleeding days (excluding spotting) and mean number of days with spotting only. See Table 18 below.
- bleeding patterns in episodes (defined as days of bleeding/spotting or spotting only that were preceded and followed by at least 2 bleed free days):
  - the mean length of bleeding/spotting episode decreased from 10.14 days in reference period 1 to 4.15 days in reference period 20; the mean length of spotting only episodes remained consistent over the study (3.96 days in the period one to 3.10 in period 20).
  - a gradual decrease in the mean number of bleeding/spotting episodes was observed (3.6 in reference period 1 to 2.2 in reference period 20), whilst the mean number of spotting only episodes was similar over the study (1.5 in reference period 1 and 1.2 in reference period 20). See Table 19 below.

Table 18. Study PH-37274 Bleeding patterns in days by 90 day reference periods (All subjects treated with LCS16, FAS)

		BLEEDING/SPOTTING days		BLEEDING ONLY days		SPOTTING ONLY days	
90-day reference period	No. of subjects	Mean (SD)	Median	Mean (SD)	Median	Mean (SD)	Median
1	1348	39.7 (19.2)	39.0	17.7 (13.2)	15.0	21.9 (14.0)	20.0
2	1300	21.1 (15.1)	19.0	8.7 (9.1)	7.0	12.3 (10.4)	10.0
3	1238	16.3 (12.8)	15.0	6.3 (7.5)	4.0	10.0 (8.8)	8.0
4	1175	14.3 (11.8)	12.0	5.1 (6.6)	3.0	9.1 (8.2)	8.0
5	1127	12.6 (11.1)	11.0	4.3 (6.0)	1.0	8.3 (8.2)	7.0
6	1102	12.3 (11.0)	10.0	4.1 (6.0)	1.0	8.2 (8.0)	7.0
7	1029	11.1 (10.0)	9.0	3.7 (5.4)	1.0	7.5 (7.2)	6.0
8	1001	11.3 (10.1)	10.0	4.0 (5.6)	1.0	7.3 (7.1)	6.0
9	927	10.8 (10.1)	9.0	3.6 (5.6)	1.0	7.2 (7.1)	6.0
10	902	10.5 (10.0)	8.0	3.5 (5.5)	0.0	7.0 (6.9)	5.0
11	858	10.4 (9.6)	9.0	3.3 (5.2)	0.0	7.1 (6.9)	6.0
12	824	10.4 (9.6)	9.0	3.4 (5.5)	1.0	7.0 (6.8)	6.0
13	617	9.6 (9.0)	8.0	3.1 (4.8)	0.0	6.6 (6.4)	5.0
14	674	9.7 (9.0)	9.0	3.1 (5.0)	0.0	6.6 (6.4)	5.0
15	638	9.3 (8.5)	8.0	2.9 (4.8)	0.0	6.4 (6.1)	5.0
16	627	9.1 (8.5)	8.0	3.0 (4.9)	0.0	6.1 (6.0)	5.0
17	595	9.1 (8.8)	7.0	2.9 (5.1)	0.0	6.2 (6.0)	5.0
18	588	9.2 (8.9)	8.0	3.0 (5.5)	0.0	6.2 (6.0)	5.0
19	550	9.2 (8.8)	8.0	2.9 (5.0)	0.0	6.3 (6.2)	5.0
20	531	9.3 (8.8)	8.0	2.9 (4.9)	0.0	6.4 (6.1)	5.0

Table 19. Study PH-37274 Bleeding patterns (bleeding/spotting) in episodes by 90 day reference periods (All subjects treated with LCS16, FAS)

		BLEEDING/SPOTTING episodes		
90-day reference period	No. of subjects	Mean length (days) (SD)	Mean maximum length (SD)	Mean range of length(SD)
1	1309	10.14 (8.91)	16.4 (12.1)	11.2 (10.3)
2	1227	6.28 (4.19)	9.3 (6.4)	5.6 (5.9)
3	1121	5.72 (5.03)	8.0 (6.7)	4.3 (5.2)
4	1019	5.29 (4.04)	7.2 (5.4)	3.7 (4.3)
5	947	4.92 (3.22)	6.5 (5.1)	3.1 (4.5)
6	918	4.93 (3.10)	6.5 (4.4)	2.9 (3.9)
7	830	4.60 (2.61)	6.1 (4.1)	2.8 (3.7)
8	815	4.78 (3.76)	6.2 (6.2)	2.8 (5.5)
9	731	4.50 (2.30)	6.0 (3.7)	2.8 (3.5)
10	732	4.47 (2.56)	5.8 (4.0)	2.5 (3.5)
11	687	4.45 (2.57)	5.8 (3.9)	2.5 (3.3)
12	658	4.52 (2.78)	5.8 (4.0)	2.4 (3.2)
13	482	4.15 (2.09)	5.4 (3.3)	2.4 (3.0)
14	529	4.31 (2.42)	5.4 (3.2)	2.0 (2.6)
15	499	4.16 (2.24)	5.3 (3.1)	2.1 (2.6)
16	485	4.24 (2.51)	5.2 (3.2)	2.0 (2.5)
17	463	4.16 (2.29)	5.3 (3.3)	2.1 (2.9)
18	454	4.16 (2.25)	5.1 (3.2)	1.8 (2.7)
19	427	4.26 (2.12)	5.3 (2.9)	1.9 (2.4)
20	411	4.15 (2.18)	5.1 (2.8)	1.8 (2.1)

Bleeding Indices as per WHO categories: Over the course of the study, there was a reduction in prolonged bleeding, frequent bleeding and irregular bleeding whilst an increase in amenorrhoea and infrequent bleeding was observed, as shown below in Table 20.

Table 20. Percentage of subjects with clinically important bleeding as per WHO categories and 90 day reference period (All subjects treated with LCS16, FAS)

Bleeding parameter	Reference period 1	Reference period 4	Reference period 20
Prolonged bleeding	56.6	5.8	1.1
Frequent bleeding	24.6	4.2	2.3
Irregular bleeding	42.5	16.7	9.4
Infrequent bleeding	10.4	26.6	26.4
Amenorrhoea	0.2	12.7	22.6
Normal bleeding (none of the above terms)	18.5	38.8	39.1

Return to fertility

Follow-up information is provided for 163 of the 179 women in the LCS16 treatment arm who discontinued due to wish for pregnancy (n = 62 in the extension phase). Of these 163 women, 116 (71.2%) became pregnant within the 12 month follow up period, with 61 (37.4%) conceiving within 3 months following LCS16 removal. At the time of contact from study sites, 4 of the 163 women were using contraception at the time (note, there was no further information provide regarding contraceptive type, duration of use or compliance). If these women are

excluded from the analysis, 73.0% became pregnant within 1 year of discontinuing treatment. There was no information provided regarding pregnancy outcomes.

At the 3 month contact, 99 women of the total LCS16 population who were contacted reported pregnancies; 61 of these women had discontinued prematurely due to wish for pregnancy as above. None of these 99 pregnancies were considered on-treatment pregnancies. The sponsor states there were 4 post-study pregnancies with unclear conception dates (n = 3 from 3 year study and n = 1 from the extension phase). All women had negative pregnancy tests at the time of LCS16 removal. These women were lost to follow up. These pregnancies were not considered as on-treatment pregnancies.

User satisfaction questionnaire

3 year data (Study A52238): The clinical evaluator for the Jaydess submission stated overall, 77.4% of subjects were 'very satisfied' with the study treatment.[4]

5 year data (Study PH-37274): Data were available for 686 subjects at the end of the extension phase at Visit 14 (subjects who completed or prematurely discontinued in the extension phase). Overall, 88.9% of subjects were 'very satisfied' with the study treatment after 5 years. The majority of subjects (94.3%) reported a reduction in menstrual bleeding, with 57.3% 'very satisfied' and 22.3% 'somewhat satisfied' with menstrual bleeding pattern.

6.3. Other efficacy studies

6.3.1. Study 308901 (CSR A46796)

Study A46796 was evaluated in the original submission for Jaydess. In summary, Study A46796 was a Phase II, multicentre, open label, randomised, dose finding study to investigate LCS12 (n = 239) and LCS16 (n = 245) compared to Mirena (n = 254) in nulliparous and parous women in need of contraception for 3 years. The study was conducted at multiple sites in 5 European countries from 2005 to 2008. The primary variable was unintended pregnancy, calculated as the Pearl Index and cumulative failure rate.

The study population included women in generally good health aged 20 to 41 years inclusive in need of contraception (FAS = 738). The clinical evaluator for the previous Jaydess submission stated the inclusion and exclusion criteria were almost identical to the pivotal Study A52238. The majority of subjects were Caucasian (733/738), with mean age 32.1 years, mean BMI 24.4 kg/m^2; 21.5% were nulliparous. The Delegate noted the demographic and baseline characteristics of treatment groups were comparable.

Comment: There were some differences in the composition of the LCS16 formulation used in Study A46796 and the formulation used in the Phase III Study 91665/310442 (the latter consistent with the to-be-marketed formulation). See Table 28.

No major protocol deviations were reported. There were 208 subjects (28.2%; comparable across the treatment groups) who discontinued prematurely, primarily due to adverse events. The Delegate commented the IUS was in the correct position in the uterine cavity in > 96% of women in all groups, with no difference in correct position of the IUS seen between parous and nulliparous women. Total exposure was similar across the treatment groups: LCS12 = 601.68 WY, LCS16 = 611.48 WY and Mirena = 627.94 WY.

There were 6 pregnancies observed during treatment:

- LCS16 = 5 (n = 2 ectopic pregnancy, n = 1 spontaneous abortion, n = 1 normal pregnancy resulting from an unnoticed expulsion)
- LCS12 = 1 (ectopic pregnancy).
- Mirena = no pregnancies.

Most pregnancies occurred in Year 2 (LCS16 = 3, LCS12 = 1) with one pregnancy in Year 1 and one pregnancy in Year 3 (LCS16 group).

The unadjusted Pearl Indices were (see Table 21 below):

- LSC16 = 0.82 (95% CI: 0.27, 1.92).
- LSC12 = 0.17 (95% CI: 0.00, 0.93).
- Mirena = 0.00 (95% CI: 0.00, 0.59).

Table 21. Study A46796 Unadjusted Pearl Indices

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

WY = women years (1WY = 365 days), CIL = confidence limit interval
Note: the relevant exposure was calculated from the total exposure minus the time in which backup contraception was used with a frequency of 'often' or 'every time.

The cumulative failure rate (Kaplan-Meier analysis) over 3 years was 0.025 for LCS16, 0.005 for LCS12 and 0.000 in the Mirena group. The clinical evaluator for the previous Jaydess submission noted the adjusted calculations were similar.

Comment: This is a Phase II dose-finding study and the EMA requirement for efficacy is a sample size sufficiently large such that the difference between the point estimate for the Pearl Index and the upper limit of the 95% CI should not exceed 1. This was met for the 3 year Pearl Index for LCS12 and Mirena. This requirement was not met for LCS16 for any time point. For LCS12, this was not met at other time points except for the Year 1. Overall the sample sizes for each arm are small, reflected in the wide CIs, and the study is not considered adequately powered to meet the requirement for efficacy.

6.4. Analyses performed across trials: pooled and meta analyses

The sponsor has provided a pooled analysis for LCS16 and LCS12 from the Phase II Study A46796 and the Phase III LCS16 efficacy study to provide additional information regarding Pearl Index calculations, bleeding data and IUS location within the uterine cavity. The number of subjects in the FAS by study and treatment is shown below in Table 22.

Table 22. Numbers of subjects in the full analysis population by study and study treatment

	LCS16	LCS12	Mirena
LCS16 Efficacy Study	1452	1432	-
Phase 2 Study [a]	245	240	256
Pooled data	1697	1672	256

a Study report excluded women with unsuccessful insertion from the FAS: 1 in the LCS12 and 2 in the Mirena group (Module 5.3.5.1, A46796, Section 7.1 and 7.2)

Comment: The pooled analysis is driven primarily by the Phase III LCS16 efficacy study. Given the Phase II study was not powered for efficacy, and the different study design and formulations used in the two studies, the pooled analysis is not considered necessary for efficacy evaluation. Proof of efficacy has been demonstrated in the pivotal Phase III LCS16 efficacy study.

6.5. Evaluator's conclusions on clinical efficacy

The pivotal Phase III LCS16 efficacy study provided data for 1452 women, 707 of which continued in to the 5 year extension phase. The overall LCS16 study population included healthy women aged 18 to 35 years, mostly Caucasian, with mean age 27.1 years, mean BMI 25.3 kg/m^2. There were 39.5% of women who were nulliparous. The study population is considered representative of the target population for marketing.

There were 13 pregnancies over the course of the study. The primary efficacy endpoint was the overall Pearl Index, which was 0.29 (95% CI: 0.16, 0.50). The Pearl Indices for each year ranged from 0.15 to 0.45 with no trend in the Pearl Index observed over time. All Pearl Indexes met the EMA guidelines efficacy requirement that the difference between the point estimate for the Pearl Index and the upper 95% CI limit should not exceed 1. The cumulative failure rate over the 5 years was 1.4%.

The Pearl Indices for subgroups stratified by age, parity and BMI were generally similar to the overall population. It is noted the number of subjects in the BMI subgroup ≥ 30 kg/m^2 was small by comparison. Although the PI and upper limit of the 95% CI met EMA efficacy guideline requirements (that the difference between the point estimate for the Pearl Index and the upper 95% CI limit should not exceed 1; Pearl Index 0.56, 95% CI: 0.15, 1.42), the upper limit of the 95% CI was above 1. Whilst a wide confidence interval can reflect the small sample size, it is difficult to draw conclusions regarding efficacy in this subgroup. See Clinical Questions below.

The bleeding profile for LCS16 is considered favourable, with an increase in amenorrhoea and infrequent bleeding over time, together with a reduction in prolonged and frequent bleeding. Return to fertility data demonstrate over 70% of women who ceased LCS16 due to desire for pregnancy conceived within 12 months after removal of LCS16.

Overall, proof of efficacy is considered demonstrated.

7. Clinical safety

7.1. Studies providing evaluable safety data

7.1.1. Pivotal studies that assessed safety as the sole primary outcome

No studies assessed safety as the sole primary outcome.

7.1.2. Pivotal and/or main efficacy studies

The pivotal Phase III LCS16 efficacy Study (Protocol) 91665/310442 and the comparative Phase II Study (protocol) 308901, as presented for demonstration of contraceptive efficacy, are relevant for safety. These studies were also submitted to support the registration of Jaydess. Please read the CER and Delegate's overview of Jaydess together with this report [details of which are available via the AusPAR/Attachment 2].[4] Only the data that are not reviewed in those reports are evaluated in this report. However, all relevant information from that report is also referred to in the current report.

All women who were enrolled and had an insertion attempt were included in the safety analysis.

The pooled analysis of the two studies in relation to the adverse event profile is included in the previous submission. The current report, mostly, refers to the individual studies rather than the pooled analysis as the design and objectives of the studies were different.

7.1.2.1. The Phase III LCS16 efficacy study

This study was designed to assess the safety and contraceptive efficacy of two doses of a LNG releasing IUS (LCS12 and LCS16) originally for a maximum of three years but extended later up to five years (extension phase for LCS16 only).

The comparative data between the two devices at three years is briefly discussed below before the uncontrolled data of LCS16 at 5 years.

Table 23. Extent of total exposure in women-years (FAS)

	LCS12	LCS16
Overall	N = 1432	N = 1452
Total exposure in WY	3218.95	3353.42

N = number of women, numbers = total exposure in women years (WY) based on the unadjusted Pearl Index (1WY = 365 days)

Regarding insertion and removal of the IUS, insertion was successful at the first attempt in 2770/2884 women (96%). A second insertion was attempted in 106/114 women who had a failed first insertion and was successful in 101 of them (95.3%). The vast majority of procedures were assessed as easy by the investigator, and most women experienced no pain or only mild pain during insertion (65%) and removal (82%). There was no significant change between groups.

A total of 2440 (84.6%) women reported at least 1 AE during this study, that is, 83.4% of the LCS12 group and 85.8% of the LCS16 group. A total of 21.1% of all women discontinued the study drug due to an AE; that is 22.3% of the LCS12 group and 20.0% of the LCS16 group.

There was a trend to reducing number of AEs over the years. The percentage of women reporting no AE increasing from around 27% for both LCS treatment arms in the first year to around 44% to 52% in treatment Years 2 and 3 for the two treatment groups respectively.

The percentage of AEs (MedDRA SOC) is listed below in Table 24. Infections, reproductive system and breast disorders featured in 50% of the subjects. They tended to be similar between the two treatment groups.

Table 24. Number (%) of subjects with AEs by MedDRA SOC in the pivotal study (FAS)

MedDRA SOC	LCS12 N = 1432 (100%)	LCS16 N = 1452 (100%)	Total N = 2884 (100%)
ANY EVENT	1194 (83.4%)	1246 (85.8%)	2440 (84.6%)
Infections and infestations	722 (50.4%)	736 (50.7%)	1458 (50.6%)
Reproductive system and breast disorders	681 (47.6%)	763 (52.5%)	1444 (50.1%)
Gastrointestinal disorders	335 (23.4%)	320 (22.0%)	655 (22.7%)
Skin and subcutaneous tissue disorders	242 (16.9%)	254 (17.5%)	496 (17.2%)
Nervous system disorders	200 (14.0%)	221 (15.2%)	421 (14.6%)
Psychiatric disorders	173 (12.1%)	172 (11.8%)	345 (12.0%)
Musculoskeletal and connective tissue disorders	144 (10.1%)	187 (12.9%)	331 (11.5%)
Investigations	150 (10.5%)	158 (10.9%)	308 (10.7%)
Injury, poisoning and procedural complications	149 (10.4%)	133 (9.2%)	282 (9.8%)
General disorders and admin. site conditions	113 (7.9%)	119 (8.2%)	232 (8.0%)
Respiratory, thoracic and mediastinal disorders	71 (5.0%)	70 (4.8%)	141 (4.9%)
Surgical and medical procedures	40 (2.8%)	45 (3.1%)	85 (2.9%)
Neoplasms, benign, malignant and unspecified (incl. cysts and polyps)	45 (3.1%)	43 (3.0%)	88 (3.1%)
Immune system disorders	63 (4.4%)	66 (4.5%)	129 (4.5%)
Eye disorders	25 (1.7%)	23 (1.6%)	48 (1.7%)
Vascular disorders	20 (1.4%)	26 (1.8%)	46 (1.6%)
Renal and urinary disorders	41 (2.9%)	31 (2.1%)	72 (2.5%)
Endocrine disorders	10 (0.7%)	21 (1.4%)	31 (1.1%)
Pregnancy, puerperium and perinatal conditions	6 (0.4%)	10 (0.7%)	16 (0.6%)
Ear and labyrinth disorders	16 (1.1%)	14 (1.0%)	30 (1.0%)
Hepatobiliary disorders	8 (0.6%)	11 (0.8%)	19 (0.7%)
Metabolism and nutrition disorders	18 (1.3%)	17 (1.2%)	35 (1.2%)
Blood and lymphatic system disorders	16 (1.1%)	8 (0.6%)	24 (0.8%)
Cardiac disorders	9 (0.6%)	14 (1.0%)	23 (0.8%)

MedDRA = Medical Dictionary for Regulatory Activities, Version 14.0, SOC = System organ class
Source: Table 14.3.1/9

The most frequently reported AEs (≥ 3%) in the FAS of LCS12 versus LCS16 were: ovarian cyst 13.0% versus 20.9%; acne 11.4% versus 11.6%; UTI 11% versus 10%; headache 9.3% versus 9.4%; dysmenorrhoea 9.1 versus 7.4%; abdominal pain 7.0% in both groups; pelvic pain 6.7% versus 8.5%; vaginal haemorrhage 4.6% 5.0%; increased weight 3.9% versus 4.7%; vaginal infection 3.4% versus 4.1%. The increase incidence of ovarian cyst was attributed to the protocol requirement for ultrasound findings of cysts to be reported as AEs even if standard AE criteria were not met). Apart from this event, there are no clinically significant differences observed between groups.

Intensity of adverse events is as follows. As seen in the following Table they were similar between groups.

Table 25. Number (%) of subjects with AEs by intensity and treatment group (FAS)

Intensity	LCS12 N = 1432 (100%)	LCS16 N = 1452 (100%)	Total N = 2884 (100%)
ANY EVENT	1194 (83.4%)	1246 (85.8%)	2440 (84.6%)
Mild	313 (21.9%)	353 (24.3%)	666 (23.1%)
Moderate	616 (43.0%)	633 (43.6%)	1249 (43.3%)
Severe	261 (18.2%)	250 (17.2%)	511 (17.7%)

The AE 'procedural pain' was reported much more frequently in Year 1 and often related to the IUS insertion LCS12: 3.4% and LCS16: 3.0%, and additionally in 0.6% of women in Year 2 and in Year 3 (generally due to non IUCD related events). This was considered study related in LCS12: 2.0%, LCS16: 1.7%.

No decrease was seen in mean bone mineral density measurements, taken in a subset of 205 subjects at lumbar spine and total hip at baseline and at 3 annual visits.

Table 26 shows drug related AEs occurring in ≥ 2.0%; Table 27 depicts the percentage of frequent SAEs. There were no clinically significant differences in the two groups, except for ovarian cyst 13.8% versus 7.7%.

Drug related SAEs are tabulated in Table 28. The incidence in the treatment groups were similar, with a slightly higher percentage of women in the LCS16 group than in the LCS12 group reporting SAEs (4.9% compared with 4.6%).

All ectopic pregnancies and all perforations (cervix or uterus) were to be reported as SAEs.

Table 26. Drug related AEs occurring in ≥ 2.0% of either group by PT (FAS)

MedDRA preferred term	LCS12 N = 1432 (100%)	LCS16 N = 1452 (100%)	Total N = 2884 (100%)
Ovarian cyst	110 (7.7%)	201 (13.8%)	311 (10.8%)
Acne	144 (10.1%)	144 (9.9%)	288 (10.0%)
Dysmenorrhea	98 (6.8%)	76 (5.2%)	174 (6.0%)
Pelvic pain	68 (4.7%)	87 (6.0%)	155 (5.4%)
Vaginal hemorrhage	65 (4.5%)	69 (4.8%)	134 (4.6%)
Headache	47 (3.3%)	48 (3.3%)	95 (3.3%)
Abdominal pain	48 (3.4%)	37 (2.5%)	85 (2.9%)
Weight increased	34 (2.4%)	48 (3.3%)	82 (2.8%)
Uterine spasm	28 (2.0%)	37 (2.5%)	65 (2.3%)
Abdominal pain lower	30 (2.1%)	31 (2.1%)	61 (2.1%)
Vaginal discharge	28 (2.0%)	28 (1.9%)	56 (1.9%)
Breast tenderness	21 (1.5%)	30 (2.1%)	51 (1.8%)
Procedural pain	28 (2.0%)	24 (1.7%)	52 (1.8%)

MedDRA = Medical Dictionary for Regulatory Activities, Version 14.0
N = total number of subjects
n = number (%) of women with drug-related AE

Table 27. Most frequent SAEs by treatment group (FAS)

Most frequent SAEs	LCS12 N = 1432 (100%) n (%)	LCS16 N = 1452 (100%) n (%)
Any SAE	**66 (4.6%)**	**71 (4.9%)**
Appendicitis	6 (0.4%)	7 (0.5%)
Abdominal pain	5 (0.3%)	4 (0.3%)
Ectopic pregnancy or ruptured ectopic pregnancy	3 (0.2%)	7 (0.5%)
Pelvic inflammatory disease	2 (0.1%)	4 (0.3%)
Ovarian germ cell teratoma benign	2 (0.1%)	2 (0.1%)
Cholecystitis	2 (0.1%)	2 (0.1%)
Spontaneous abortion, incomplete spontaneous abortion, or blighted ovum	3 (0.2%)	2 (0.1%)
Pneumonia	2 (0.1%)	1 (<0.1%)
Ovarian cyst	1 (<0.1%)	2 (0.1%)
Cholelithiasis	1 (<0.1%)	2 (0.1%)
Urinary tract infection	2 (0.1%)	0
Thyroid cancer	2 (0.1%)	0
Haemorrhagic ovarian cyst	2 (0.1%)	0
Goitre	1 (<0.1%)	1 (<0.1%)
Pyelonephritis	1 (<0.1%)	1 (<0.1%)
Cellulitis	1 (<0.1%)	1 (<0.1%)
Peritonsillar abscess	1 (<0.1%)	1 (<0.1%)
Anxiety	1 (<0.1%)	1 (<0.1%)
Depression	1 (<0.1%)	1 (<0.1%)
Ovarian cyst ruptured	1 (<0.1%)	1 (<0.1%)
Asthma	1 (<0.1%)	1 (<0.1%)
Detoxification	1 (<0.1%)	1 (<0.1%)
Procedural pain	0	2 (0.1%)
Dizziness	0	2 (0.1%)

Table 28. Study drug related SAEs by treatment group (FAS)

Study drug-related SAEs	LCS12 N = 1432 (100%) n (%)	LCS16 N = 1452 (100%) n (%)
Any SAE	**66 (4.6%)**	**71 (4.9%)**
Any study drug-related SAE	**8 (0.6%)**	**15 (1.0%)**
Ectopic pregnancy	2 (0.1%)	6 (0.4%)
Pelvic inflammatory disease	2[b] (0.1%)	4 (0.3%)
Abdominal pain	1 (<0.1%)	2[c] (0.1%)
Device dislocation (partial myometrial perforation)	0	1 (<0.1%)
Tubo-ovarian abscess	1[b] (<0.1%)	0
Spontaneous abortion	1[a] (<0.1%)	0
Incomplete spontaneous abortion	0	1[c] (<0.1%)
Premature separation of placenta	1[a] (<0.1%)	0
Ruptured ectopic pregnancy	0	1 (<0.1%)
Hemorrhagic ovarian cyst	1 (<0.1%)	0
Ovarian cyst	0	1 (<0.1%)
Ovarian cyst ruptured	1 (<0.1%)	0

Source: Table 14.3.1/18
NOTE: Numbers of individual MedDRA 14.0 PTs do not add up to total number of study drug-related SAEs as some subjects had more than one SAE coded for the event that had happened:

Adverse events of special interest

Ovarian cyst (MedDRA PT): This was reported for LCS12 (13.0%) and in LCS16 (20.9%). According to protocol, ovarian cysts were to be reported as AEs if they were abnormal non-functional cysts and/or had a diameter > 3 cm on ultrasound. Since the protocol required repeated vaginal ultrasound, incident ultrasound findings of cysts > 3cm were therefore documented as AEs. These events were reported as mild in 10.8% of the women in the LCS12 group and 17.0% of the women in the LCS16 group, moderate in 1.7% and 3.4% respectively, and severe in 0.5% women of each of the two groups.

Ovarian cyst was reported as an SAE in 3 women (LCS12: 1, LCS16: 2), ruptured ovarian cysts in one woman per group; 2 women of the LCS12 group had haemorrhagic ovarian cysts reported as SAEs, and one woman of the LCS16 group had an ovarian cyst torsion reported.

PID: PID was diagnosed in 12 women in total; of the 12 women diagnosed with PID, a total of 7 (LCS12: 4, LCS16: 3) had an acute salpingo-oophoritis diagnosed, a total of 3 (LCS12: 2, LCS16: 1) had a tubo-ovarian abscess, and 2 subjects had no specification of PID diagnosis reported. Six of these were SAEs relating to PID (2 in LCS12, and 4 in LCS16). All patients recovered. Two subjects who did not appear to meet the protocol specified criteria for PID (each had only 1 of the signs or symptoms outlined in the protocol criteria for PID), but had this diagnosis reported but were not withdrawn from the study. In both cases, the event occurred in the first year of treatment and resolved without sequelae.

Perforation of the uterus: One partial perforation of the myometrium by the LCS was reported in the LCS16 group. The LCS was removed via the vagina, with no further complications. In this study, a 28 year old nulliparous woman had a partial uterine perforation detected in Month 24 via ultrasound. The insertion was rated as easy by the investigator; no dilatation was performed, no anaesthesia/analgesics given. The patient's evaluation of pain was 'severe'.

Endometritis: A total of 0.8% of subjects in the LCS12 and LCS16 arms in this study were diagnosed with endometritis. These were not considered as suspicious for PID by the investigators based on clinical presentation. Most events were moderate in severity (13 of 22),

one was severe, and the events occurred most frequently in parous women and during the first year of the study.

Ectopic pregnancies: There were 3 reports in the LCS12 group and 7 in the LCS 16 group. Nulliparous was 2 and 3 in each group respectively and those aged 26 to 35 years was 1 and 5 in each group respectively. All were Caucasians. There were 2 in the LCS12 group and 7 in the LCS16 group stated to be study related.

Device expulsion: Expulsion occurred in >3% (3.4%) of all subjects, 53 for LCS12 (3.7%) and 46 for LCS16 (3.2%).

Device dislocation: AEs were reported for 2 women (0.1%) in the LCS12 group and 4 women (0.3%) in the LCS16 group (overall in 6 or 0.2% of women). One of the dislocation events was a partial perforation of the myometrium (an SAE) and the others were reported as 'displaced, intrauterine' or 'displaced, cervical canal'.

Bleeding: Amenorrhoea rate gradually increased over the course of the 3 year study to 11.4% in the LCS12 group and 20.8% in the LCS16 group in the twelfth 90 day reference period. The no bleeding rate (excluding spotting) rose to 39.0% in the LCS12 group and 49.9% in the LCS16 group in the same period.

Deaths: None related to the study medications, see the AusPAR/Attachment 2 for the Jaydess submission.[4]

No clinically meaningful changes in laboratory values or vital signs were seen in either treatment group.

The AEs that most frequently led to withdrawal of study medication were vaginal haemorrhage (3.3%), device expulsion (2.8%), pelvic pain (2.4%), acne (2.2%), abdominal pain and dysmenorrhea (1.1% each). The treatment groups were affected similarly, with acne more frequent in the LCS12 group and pelvic pain slightly more frequent in the LCS16 group.

The five year data based on Report PH-37274 where LCS16 was extended to 5 years is as follows in Table 29.

Table 29. Extent of exposure, all subjects treated with LCS16 (FAS)

	No-extension group N = 745 (100%)	Extension group N = 707 (100%)	Total N = 1452 (100%)
Treatment duration (days)			
Mean (SD)	603.6 (377.5)	1745.8 (173.3)	1159.8 (643.3)
Min, Max	1, 1248	1083, 1953	1, 1953
Woman years [a]			
Mean (SD)	1.65 (1.03)	4.78 (0.47)	3.18 (1.76)
Min, Max	0, 3.4	3.0, 5.4	0, 5.4
Total	1232.05	3381.55	4613.61

FAS = Full analysis set; N = Total number of subjects (100%)
a: A woman-year equals 365 days

Among subjects on LCS16, 994 (68.5%) experienced AEs with maximum intensity of mild or moderate. In 279 subjects (19.2%), the maximum intensity of AEs was classified as severe. AEs by SOC are shown in Table 30.

The most frequent drug-related AEs experienced by subjects treated with LCS16 were: ovarian cyst (15.7%), acne (10.2%), pelvic pain (6.3%), dysmenorrhea (5.4%) and vaginal haemorrhage (5.0%).

Drug-related AEs (≥ 2%) are found in Table 31. The overall incidence at 5 years tended to be low: ovarian cyst 15.7%, acne 10.2%, pelvic pain 6.3% and headache 3.5%. SAEs considered study drug related are shown in Table 32.

Table 30. Incidence of AEs by MedDRA SOC (All subjects treated with LCS16, FAS)

MedDRA SOC[a, b]	Total N = 1452(100%) n (%)
Any AE	**1286 (88.6%)**
Reproductive system and breast disorders	828 (57.0%)
Infections and infestations	786 (54.1%)
Gastrointestinal disorders	355 (24.4%)
Skin and subcutaneous tissue disorders	280 (19.3%)
Nervous system disorders	237 (16.3%)
Musculoskeletal and connective tissue disorders	226 (15.6%)
Psychiatric disorders	206 (14.2%)
Investigations	186 (12.8%)
Injury, poisoning and procedural complications	159 (11.0%)
General disorders and admin. site conditions	146 (10.1%)
Respiratory, thoracic and mediastinal disorders	82 (5.6%)
Immune system disorders	78 (5.4%)
Neoplasms, benign, malignant and unspecified (incl. cysts and polyps)	64 (4.4%)
Surgical and medical procedures	54 (3.7%)
Renal and urinary disorders	39 (2.7%)
Vascular disorders	29 (2.0%)
Eye disorders	26 (1.8%)
Endocrine disorders	25 (1.7%)
Ear and labyrinth disorders	20 (1.4%)
Metabolism and nutrition disorders	21 (1.4%)
Cardiac disorders	17 (1.2%)
Hepatobiliary disorders	13 (0.9%)
Pregnancy, puerperium and perinatal conditions	12 (0.8%)
Blood and lymphatic system disorders	10 (0.7%)

AE = Adverse event; FAS = Full analysis set; MedDRA = Medical Dictionary for Regulatory Activities; SOC =System organ class; N = Total number of subjects (100%); n = Number of subjects with event
a: A subject is counted only once within each preferred term of any primary SOC.
b: Not displayed are congenital, familial and genetic disorders as well as social circumstances with 0.1% or less of subjects involved overall.

Table 31. Drug related AEs occurring in ≥ 2.0% by MedDRA PT (All subjects treated with LCS16, FAS)

MedDRA preferred term	Total N = 1452 (100%) n (%)
Any AE	**1286 (88.6%)**
Drug-related AE	**803 (55.3%)**
Ovarian cyst	228 (15.7%)
Acne	148 (10.2%)
Pelvic pain	92 (6.3%)
Dysmenorrhea	79 (5.4%)
Vaginal hemorrhage	73 (5.0%)
Weight increased	51 (3.5%)
Headache	50 (3.4%)
Abdominal pain	39 (2.7%)
Abdominal pain lower	38 (2.6%)
Uterine spasm	37 (2.5%)
Breast tenderness	33 (2.3%)
Vaginitis bacterial	32 (2.2%)
Device expulsion	30 (2.1%)

FAS = Full analysis set; MedDRA = Medical Dictionary for Regulatory Activities, Version 16.0; N = total number of subjects; n = number (%) of women with drug-related AE

Table 32. Study drug related SAEs (All subjects treated with LCS16, FAS)

Study drug-related SAEs by MedDRA PT	Total N=1452 (100%) n (%)
Any SAE	**86 (5.9%)**
Any study drug-related SAE	**19 (1.3%)**
Ectopic pregnancy	7 (0.5%)
Pelvic inflammatory disease	5 (0.3%)
Abdominal pain [a]	2 (0.1%)
Abortion missed	1 (<0.1%)
Abortion spontaneous incomplete [a]	1 (<0.1%)
Device dislocation [c]	1 (<0.1%)
Ovarian cyst	1 (<0.1%)
Ruptured ectopic pregnancy	1 (<0.1%)
Uterine perforation [d]	1 (<0.1%)

NOTE: Numbers of individual MedDRA 16.0 PTs do not add up to total number of study drug-related SAEs as some subjects had more than one SAE coded for the event that had happened

Drug related withdrawals (≥ 1%): vaginal haemorrhage 3.3%; pelvic pain 2.5%; device expulsion 2.1% and acne 1.8%.

Device expulsions: total or partial expulsions were documented for 54 subjects (3.7%) treated with LCS16.

Uterine perforation: 2 additional reports (after the 3 year period) were included. The devices were removed transvaginally and the patients recovered without sequelae.

Endometritis was reported for 0.9% subjects, PID 0.5% subjects and salpingo-oophoritis 0.2% subjects. These appeared randomly and did not relate to duration.

There was one additional report of ectopic pregnancy in the 4 to 5 year period.

Laboratory abnormalities were not clinically significant.

7.1.2.2. CSR Study A46796 (Protocol 308901)

'Multicentre, open, randomised, dose finding Phase II study to investigate for a maximum of 3 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' (see also the AusPAR/Attachment 2 for the previous Jaydess submission).[4]

Extent of exposure is shown in the following table.

Table 33. Extent of total exposure by study phase in women years (FAS)

	LCS12	LCS16	Mirena
Year 1	N = 239	N = 245	N = 254
Total exposure in WY	226.07	233.30	239.35
Year 2	N = 215	N = 215	N = 219
Total exposure in WY	196.48	197.93	201.06
Year 3	N = 187	N = 189	N = 193
Total exposure in WY	176.25	177.25	184.75
Overall	N = 239	N = 245	N = 254
Total exposure in WY	601.68	611.48	627.94

N = number of women, numbers = total exposure in women years (WY) based on the unadjusted Pearl Index (1WY = 365 days)

An overview of AEs is found below in Table 34. 89% of subjects reported at least 1 AE. AEs tended to reduce with time in all groups. In the LCS16 group the incidence in the first year was 81% and reduced by the third year to 51%.

Table 34. Study A46796 (Phase II), protocol 308901

Subjects	LCS12 N = 239	LCS16 N = 245	Mirena N = 254	Total N = 738
With at least 1 AE (total years 1-3)	208 (87.0%)	220 (89.8%)	232 (91.3%)	660 (89.4%)
With any AE of severe intensity	33 (13.8%)	37 (15.1%)	36 (14.2%)	106 (14.4%)
With any drug-related AE[a]	162 (67.8%)	163 (66.5%)	184 (72.4%)	509 (69.0%)
With any SAE	12 (5.0%)	12 (4.9%)	16 (6.3%)	40 (5.4%)
Who discontinued study drug due to AE	42 (17.5%)	46 (18.8%)	48 (18.9%)	136 (18.4%)
Who died	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

N = total number of patients. Patients are counted more than once in this table.
[a] AEs reported to be at least possibly related

As in the previous study, AEs were reported most frequently in the following system organ classes: reproductive system and breast disorders (54.1%), and infections and infestations: women (48.4%). There were no significant changes in the LCS groups.

The most frequently reported AEs by preferred term were: headache (28.2%), acne (26.8%), breast discomfort (22.4%), abdominal distension (18.8%), mood altered (15.0%), ovarian cyst (14.8%), weight increased (14.6%), breast pain (11.1%) and vulvovaginal candidiasis (10.0%). Abdominal pain (8.4%) and lower abdominal pain (7.6%) were recorded as separate terms. All other terms were reported in fewer than 10% of women. Of interest were procedural pain (8.5%) which in most cases referred to insertion related pain, nausea (8.1%), oedema (7.5%) and seborrhoea (7.5%), which occurred in a smaller proportion of women in the LCS groups than in the Mirena group.

Of the 660 women who experienced at least 1 AE, (14.4%) reported AEs that were rated by the investigator as severe in intensity. For 22.1% the maximum intensity of AEs was mild and for 52.2% the maximum intensity was moderate. The distribution of women with mild, moderate and severe events was approximately equal among the treatment groups. The AEs most frequently classified as severe were dysmenorrhea (13 women), abdominal pain (9 women), and lower abdominal pain and procedural pain (7 women each), equally distributed over the treatment groups. All other AEs of severe intensity were reported in very small numbers of women per treatment group.

The number experiencing drug related events are listed in Table 41 and the details of the events experienced (≥ 1.4%) are included in Table 42. The treatment groups were comparable with regard to drug-related AEs, with slightly more (72.4%) women in the Mirena group than in the LCS12 and LCS16 groups (67.8% and 66.5%) with drug-related AEs. The only drug-related AE that occurred considerably more often in any treatment group was ovarian cyst, which was reported for 22.0% in the Mirena group, compared with 5.9% and 8.6% in the LCS12 and LCS16 groups respectively.

Table 35. Drug related AEs occurring in ≥ 10 women (≥ 1.4%) in any treatment arm

MedDRA preferred term	LCS12 N = 239 (100%)	LCS16 N = 245 (100%)	Mirena N = 254 (100%)	Total N = 738 (100%)
Acne	62 (25.9%)	55 (22.4%)	72 (28.3%)	189 (25.6%)
Breast discomfort	46 (19.2%)	45 (18.4%)	57 (22.4%)	148 (20.1%)
Abdominal distension	33 (13.8%)	35 (14.3%)	41 (16.1%)	109 (14.8%)
Headache	28 (11.7%)	32 (13.1%)	44 (17.3%)	104 (14.1%)
Ovarian cyst	14 (5.9%)	21 (8.6%)	56 (22.0%)	91 (12.3%)
Mood altered	34 (14.2%)	25 (10.2%)	25 (9.8%)	84 (11.4%)
Weight increased	27 (11.3)	28 (11.4%)	21 (8.3%)	76 (10.3%)
Breast pain	15 (6.3%)	28 (11.4%)	18 (7.1%)	61 (8.3%)
Seborrhea	16 (6.7%)	18 (7.3%)	20 (7.9%)	54 (7.3%)
Nausea	13 (5.4%)	14 (5.7%)	17 (6.7%)	44 (6.0%)
Edema	10 (4.2%)	17 (6.9%)	17 (6.7%)	44 (6.0%)
Abdominal pain	13 (5.4%)	11 (4.5%)	14 (5.5%)	38 (5.1%)
Dysmenorrhea	12 (5.0%)	12 (4.9%)	11 (4.3%)	35 (4.7%)
Abdominal pain lower	8 (3.3%)	10 (4.1%)	11 (4.3%)	29 (3.9%)
Vulvovaginal candidiasis	10 (4.2%)	5 (2.0%)	6 (2.4%)	21 (2.8%)
Vaginal hemorrhage	9 (3.8%)	2 (0.8%)	4 (1.6%)	15 (2.0%)
Vaginal infection	5 (2.1%)	4 (1.6%)	5 (2.0%)	14 (1.9%)
Procedural pain	4 (1.7%)	4 (1.6%)	3 (1.2%)	11 (1.5%)
Vaginitis bacterial	6 (2.5%)	1 (0.4%)	3 (1.2%)	10 (1.4%)

MedDRA = Medical Dictionary for Regulatory Activities, Version 11.1
N = total number of subjects
n = number (%) of women with drug-related AE

SAEs were reported in 5% in LCS12, 4.9% in LCS16 and 5.4% in Mirena groups.

Drug related withdrawals: A total 4.2% led to the study treatment being withdrawn. The number of subjects in whom study treatment was withdrawn due to AE was comparable across the treatment groups (LCS12: 42, LCS16: 46, Mirena: 48). The numbers were too small to detect a trend.

Device insertion: IUS insertion failed in 4 women (LCS12: 1 (cervical anomaly), LCS16: 1 (technical problems), Mirena: 2 (AE vasovagal attack; cervical anomaly). 100% had an IUS inserted. There were 3 total expulsions and 2 partial expulsions in the LCS 16 group. Similar numbers were reported in other groups.

Ovarian cysts: None reported in the LCS16 group.

Ectopic pregnancy: 2 were reported in the LCS16 group. One is stated to have been withdrawn.

PID: One reported in the LCS16 group reported as withdrawn (severe).

No deaths were reported.

There were no clinically significant laboratory results.

7.2. Studies using the same Evolution Inserter

A rationale for using the safety data from 3 LCS12 studies is proffered for the sponsor in the Clinical Overview and is as follows:

> *'The Evolution Inserter has been approved as an integral part for use with LCS12 and Mirena, and is already used in many countries. The inserter was modified to simplify the preparatory steps of the IUS prior to insertion…*
>
> *Because the Evolution Inserter for LCS12 and LCS16 is of the same design and dimensions, safety data supporting the use of the Evolution Inserter for LCS16 are based on three clinical studies in which LCS12 was placed using the Evolution Inserter'.*

LCS12 studies using the evolution inserter are Protocols 13362, 13363, and 14371. These are briefly discussed in the original report (see the AusPAR/Attachment 2 for the previous Jaydess submission).[4]

Protocol 13362 was a multicentre, randomised, open label, parallel group study of LCS12 for 18 months, with an optional extension for up to 36 months. Yasmin (21 tablets containing 0.030 mg ethinylestradiol + 3 mg drospirenone followed by 7 inert tablets per 28 day cycle), oral, was the comparator. The study duration was up to 18 months or 19 cycles.

Protocol 13362 was a multicentre, open label, randomised, controlled parallel group study LCS12 12 months, optional extension for up to 3 years. Nexplanon (etonogestrel (ENG) 68 mg subdermal implant) was the comparator.

Protocol 14371 was a multicentre, open label, single group study up to 1 year LCS12 of 12 months duration with an optional extension up to 3 years.

These are only considered in relation to the safety of the inserter device as it is claimed to be the same as the device to be used in LCS16 for marketing.

A total of 279 subjects were included in the LCS12 in Protocol 13362, 382 in Protocol 13363 and 304 in the LCS12 in protocol 14371.

Demographics: In Protocols 13362 and 13363, those between the ages of 18 to 25 ranged from 63 to 68% and those of 26 to 35 years were between 31 to 37%. Those who never smoked were 59.5% to 63%. 88 to 94% were White. In the adolescent study (14371), 99.3% were less than 18 years; other characteristics were similar to the previous studies.

Parity: 73%, 63.5% and 92% were nulliparous.

Menstrual history: Average length of the cycle was 28.3 days ± 2.2. Approximately 6.8% to 27.3% (adolescent study) had heavy menstrual bleeding. Approximately 70% in the pooled data reported prior oral contraception.

Overall assessment of insertion procedure: insertion was attempted in 965 women (FAS, pooled population) and for 98.2% the insertions of LCS12 with the Evolution Inserter were successful. The insertion was successful at the first attempt in 948 women and in 12 women at the second attempt. Insertion failure was reported in 1.8% of all women (pooled analysis). Overall, no dilatation was needed for more than 60% of the women treated with LCS12 using the Evolution Inserter. If dilation was needed, it was mainly performed before the insertion attempt (18.0% of all women). There were only a few cases where dilatation was performed when the procedure proved to be difficult (9 of 960 women) or painful (1 woman).

Local anaesthesia was given in 19.2% before the insertion procedure. The use of local anaesthesia before the procedure was more common in adolescent women (31.6%) compared to adult women (20.8% and 8.1% in the LCS12 Protocol 13362 and 13363, respectively).

Insertion pain: 19% had none, 39.3% had mild, 31.6% had moderate pain and 10% had severe pain.

Pregnancies: There were 4 pregnancies (3 of them ectopic) in LCS12 Study 13362 and 3 pregnancies (1 of them ectopic) in the LCS12 Study 13362.

Any TEAE was reported in 83% in the pooled analysis; it was similar across studies. Any drug related TEAEs was 38.7%, 61.8% and 41.8% respectively. Intensity of mild, moderate and severe was 23.5%, 43.6% and 15% respectively.

PID: There was 1 report of endometritis in Study 13362 and Study 13363; there were 4 reported in study 14371

Uterine dislocation: One report of uterine dislocation in Study 13362.

Expulsion: One partial expulsion was reported in Study 13362; 3 in Study 13363 and 7 in Study 14371.

The extension phase of the two studies totalled 3 years. There were 13 SAEs; 2 were pregnancies and the others unrelated.

Another study (Protocol 91775) also provided supportive information on the safety of the device. This was a multicentre, open label, single arm study to assess efficacy, safety, bleeding pattern and pharmacokinetics of the ultra-low dose levonorgestrel intrauterine contraceptive system (LCS12) for a maximum of 3 years in women 18 to 40 years of age. There were 925 subjects included in the FAS. According to the FAS definition, all subjects for whom an insertion was at least attempted were included. LCS12 insertion failed for 7 out of the 925 subjects. 918 subjects had the LCS12 inserted, that is were treated. The FAS was used for all efficacy and safety analyses. The majority of the subjects were of Asian ethnicity (857, 92.6%). The mean age of subjects was 31.6 years (SD 4.4); range 18 to 40 years. 258 (27.8%) subjects discontinued from the study prematurely. The safety results were in line with those mentioned in the previous study.

Overall, these studies provide a crude index of safety of the device proposed for marketing.

7.3. Other safety issues

7.3.1. Safety in special populations

Please also refer to the submission for Jaydess (see the AusPAR/Attachment 2).[4]

It is noted that in relation to nulliparous women: 36.7% of the women in the LCS16 group were nulliparous with a higher percentage recorded in the pivotal study (39.5% in the LCS16 efficacy study versus 20.0% in the Phase II study). Adverse events were reported more frequently overall in nulliparous women: 93.7% of the nulliparous women in the LCS16 pool had AEs compared with 85.8% of the parous women. Acne (17.3% versus 12.3%), dysmenorrhea (11.7% versus 5.8%), pelvic pain (11.4% versus 6.1%), nasopharyngitis (10.4% versus 6.5%), and vulvovaginal mycotic infection (8.8% versus 7.1%) were specific AEs reported more frequently in nulliparous women, and the pattern was similar across treatment groups.

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

There were no specific studies submitted.

7.4. Post marketing experience

Jaydess (LCS12), though registered in Australia is not marketed here. It is noted that the results of EURAS-IUD study were discussed at the PRAC during its meeting of 7 to 10 April 2014. The PRAC recommended that the product information for Mirena and Jaydess be updated to reflect the final 1 year follow-up results of the EURAS-IUD study. In addition, the sponsor was asked to submit additional data and information, which was provided by the company together with a labelling variation in June 2014.

Actions arising from the EU Decentralised Procedure for Jaydess include additional risk minimisation measures in form of appropriate communication to raise prescribers' awareness

of the risk of ectopic pregnancy, emphasising the importance of early diagnosis, and to help to differentiate between different types of LNG IUS (with different approved duration of use) via ultrasound. Consequently, educational material to address communication measures regarding awareness of the risk of ectopic pregnancy and to help to differentiate between different types of LNG IUS (that is, Jaydess/Mirena) was developed for all EU countries included in the EU Decentralised Procedure. The educational material was nationally submitted in EU and approved depending on national regulations during 2013 and 2014, and was made available for launch in the individual EU countries during 2014.

It is stated in the PSUR that the CCDS for Jaydess was updated to include the main results of EURAS-IUD regarding uterine perforation. This included perforation rates (for the entire study population and for the Mirena and copper IUD cohorts) and an update of the existing warning on risk factors for uterine perforation in the Jaydess CCDS with numerical information deriving from EURAS-IUD on the risk factors breastfeeding, and time since last delivery. A section was modified to include information on the frequency of perforation in the populations at higher risk.

There were no other safety related issues identified in the PSUR of 2014.

In 2015 it is estimated that, over 420,000 Jaydess units were sold. The number of units sold since introduction of Jaydess to the market is close to 741,000. The estimated cumulative post-marketing exposure is estimated to be more than 774,000 woman-years for Jaydess at the time of DLP for this PBRER/PSUR. Close to 535,000 woman-years accumulated during 2015.

No further safety changes or risk minimisation activities were undertaken during this period.

7.5. Evaluator's overall conclusions on clinical safety

The pivotal study Protocol 91665 (310442) was designed to compare LCS12 and LCS16 and was the study used in the registration dossier for Jaydess, that is, the safety and efficacy of these studies have been evaluated in the previous submission.[4] The 3 year results of safety showed a trend to reducing the number of AEs over the duration. All AEs were similar between groups except for ovarian cysts which were 13.0% versus 20.9% in the LCS12 and LCS16 groups respectively. Other adverse events of special interests did not reveal any clinically significant increase in the LCS16 group. Report PH-37274 deals with the uncontrolled extension study of Protocol 91665 on 707 subjects using LCS16. Whilst these data have limited significance due to the nature of being uncontrolled in design, there were no untoward concerns identified in relation to safety.

The Phase II Study A46796, (Protocol 308901) where LCS 12 (n = 239), LCS 16 (n = 245) and Mirena (n = 254) were studied for three years, supported the safety findings of the pivotal study.

Safety of the inserter device: It is noted that the device to 'be marketed' is different to that used in the LCS16 studies that support efficacy. Three studies using this insertion device are discussed above under the section 'Clinical Safety: Studies using the same Evolution Inserter'. A total of 965 subjects have been involved and provide a crude index that the device is safe and does not provide any untoward side effects. This is considered supportive information only.

A comprehensive evaluation of the device is required from a quality point of view to recommend registration.

Overall, the safety of the LCS16 appears acceptable.

8. First round benefit-risk assessment

8.1. First round assessment of benefits

- Kyleena provides effective contraception for 5 years, a longer duration of action than the currently registered low dose LNG IUS Jaydess.
- The daily LNG release rates are lower than Mirena, the currently registered LNG IUS product which can be used for 5 years. This may theoretically be associated with a more favourable adverse effect profile, although in the absence of direct comparison to Mirena over 5 years no conclusions can be drawn.
- The bleeding profile over 5 years demonstrates a trend towards infrequent bleeding over time. Again, there is no direct comparison to Mirena over the same duration.
- Less systemic progesterone exposure than oral products therefore less risk of progesterone related adverse events.

8.2. First round assessment of risks

- Unknown risks:
  - efficacy in women with BMI ≥ 30 kg/m^2.
  - safety in MRI.
- Known risks of LNG IUS:
  - unplanned pregnancy.
  - ectopic pregnancy, expulsion, uterine perforation.
  - ovarian cyst.
  - pelvic inflammatory disease.
  - pain on insertion.
  - changes in bleeding pattern.
  - progesterone related effects.

9. Clinical questions

Q1) Pharmacokinetic data demonstrates an effect of bodyweight on the LNG clearance parameter. Both the Pearl Index and cumulative failure rate for women with BMI ≥ 30 kg/m^2 in the LCS16 efficacy study were higher than subjects with BMI < 30 kg/m^2. The small number of subjects in the BMI ≥ 30 kg/m^2 subgroup is noted; however, please comment on efficacy in this population. Are there post-marketing pregnancy data available for Jaydess in women with BMI ≥ 30 kg/m^2?

Q2) Please state whether Jaydess will be marketed together with Kyleena, in Australia? If so, what principles are to be taken to prevent medication errors? This is considered relevant because the two products have different duration of contraception as the indication.

Q3) Adverse effects included 'Table 4' [not included here] that refers to bleeding patterns at 90 days to 5 years. The types of abnormalities discussed are amenorrhoea, infrequent bleeding, frequent bleeding and prolonged bleeding. Clearly this should only include the pivotal study and its extension to 5 years. The cross reference does not appear to relate to the findings of this

study rather discusses the pooled data which is not a factual representation as the second study does not extend to 5 years.

Please provide the results for the bleeding abnormalities that relate to the pivotal study and its extension arm. Please also provide the cross reference for these findings.

Q4) What is the evidence behind the concerns about Kyleena and use in congenital or valvular heart disease?

Q5) Is there any evidence that the low systemic levels of progesterone associated with the use of Kyleena will cause problems with glucose metabolism?

Q6) Is it safe for women with a Kyleena IUD to undergo an MRI? What is the experience with similar products? Does there need to be a stronger warning against this?

Q7) Please comment on the risk of PID with Kyleena compared to the background rate of PID in sexually active women of this age without an IUD.

Q8) Please describe the evidence behind the following statement under 'Clinical Trials' of the proposed PI: 'The use of Kyleena does not alter the course of the future fertility'.

Q9) Please provide an update on overseas regulatory status for LCS16.

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

10.1. Change to proposed trade name

Of note, at the second round response to TGA questions the sponsor states the proposed trade name Sofitta has been changed to Kyleena.[1]

10.2. Response to clinical questions

10.2.1. Question 1

> *'Pharmacokinetic data demonstrates an effect of bodyweight on the LNG clearance parameter. Both the Pearl Index and cumulative failure rate for women with BMI ≥ 30 kg/m² in the LCS16 efficacy study were higher than subjects with BMI < 30 kg/m². The small number of subjects in the BMI ≥ 30 kg/m² subgroup is noted; however, please comment on efficacy in this population. Are there post-marketing pregnancy data available for Jaydess in women with BMI ≥ 30 kg/m²?'*

10.2.1.1. Sponsor's response

Pharmacokinetically, there was a body weight effect on clearance observed for Kyleena as well as for Jaydess. However, due to the mainly local mechanism of action of levonorgestrel releasing intrauterine systems (LNG IUS), the efficacy is not dependent on the BMI. When comparing the serum concentrations for Kyleena at 5 years post insertion (Geometric Mean: 83.1 ng/L; 95% CI: 78.9, 87.5 ng/L) with Jaydess at 1 year (Geometric Mean: 71.0 ng/L; 95% CI: 69.8, 72.2 g/L) and 3 years after insertion (Geometric Mean: 58.6 ng/L; 95% CI: 56.5, 60.8 ng/L), it can be observed that Kyleena serum concentrations at five years are similar, but slightly higher than for Jaydess at 1 year after insertion and clearly higher without overlapping 95% confidence intervals at 3 years after insertion. Despite these lower serum levonorgestrel concentrations observed for Jaydess, Pearl Indices for both products are similar.

In the submission, a table [not included here] summarises the number of during-treatment pregnancies in the subgroups based on age, parity status, age and parity combined, BMI and

ethnicity in the LCS16 efficacy study, Phase II study, and in the pooled data. In most cases, women with pregnancies had a BMI under 30 kg/m^2 (pooled LCS16: 14 out of 18, pooled LCS12: 10 out of 11 pregnancies). The number of subjects in the BMI ≥ 30 kg/m^2 subgroup is small. In the pivotal study, in the subgroup with BMI under 30 kg/m^2, 9 pregnancies in a total of 1198 women occurred while 4 pregnancies in a total of 250 women in the subgroup with the BMI ≥ 30 kg/m^2 occurred. Due to the small number of women in the BMI ≥30 kg/m^2, the confidence intervals for the contraceptive efficacy and the probability of getting pregnant are wider than for the larger group with the BMI under 30 kg/m^2. However, these confidence intervals overlap at all time points giving no indication that there is a difference in the contraceptive efficacy between the two BMI subgroups.

There are no post-marketing data available on pregnancy rate for Jaydess in women with a BMI ≥ 30 kg/m^2. However, there are pooled data across 6 studies with a total of 3222 women with a BMI < 30 kg/m^2 and 335 women with a BMI ≥ 30 kg/m^2 using Jaydess in the RMP Integrated Analysis (IA) [see Tables 36 and 37, included with the evaluator's response to this question, below]. Among the women with a lower BMI, there were a total of 25 pregnancies resulting in a Pearl Index of 0.39 (95% CI 0.25; 0.58), while in the subgroup with a BMI ≥ 30 kg/m^2, only 1 pregnancy occurred resulting in a Pearl Index of 0.15 (95% CI 0.00; 0.84). Furthermore, in this pooled database of 6 studies with Jaydess, the confidence intervals overlap giving no indication that there is a difference in the contraceptive efficacy between the two BMI subgroups.

10.2.1.2. Evaluator's response

The sponsor's response is considered acceptable. It is noted there are no post-marketing data regarding pregnancy rates for Jaydess in women with BMI ≥ 30 kg/m^2, although the Sponsor provided pooled data from 6 studies with Jaydess for contraceptive efficacy by BMI (Studies 91665, 308901, 13362, 13363, 91775 and 14371, discussed earlier in the body of the report). The table referred to in the response above is provided below for ease of reference. From the pooled data for Jaydess, there was 1 pregnancy in the subgroup of women with BMI ≥ 30 kg/m^2 (n = 335), resulting in a Pearl Index of 0.15 (95% CI: 0.00, 0.84). The Pearl Index meets the EMA guidance efficacy requirement that the difference between the point estimate for the Pearl Index and the upper 95% CI limit should not exceed 1.

Table 36. Contraceptive efficacy by BMI in the pooled studies (FAS): BMI ≥ 30 kg/m^2

Time	Treatment	Number of subjects	Total exposure [WY]	Excluded exposure [WY]	Relevant exposure [WY]	Number of pregnancies	Pearl Index	Lower 95% CIL	Upper 95% CIL
Overall	LCS12	335	701.95	39.90	662.04	1	0.15	0.00	0.84
	LCS16	276	818.96	31.80	787.16	4	0.51	0.14	1.30
Year 1	LCS12	335	296.70	18.99	277.71	1	0.36	0.01	2.01
	LCS16	276	247.05	11.69	235.35	1	0.42	0.01	2.37
Year 2	LCS12	260	219.55	11.64	207.91	0	0.00	0.00	1.77
	LCS16	226	206.55	6.61	199.94	2	1.00	0.12	3.61
Year 3	LCS12	199	182.22	7.97	174.25	0	0.00	0.00	2.12
	LCS16	189	173.65	3.86	169.79	1	0.59	0.01	3.28
Year 4	LCS16	133	102.96	4.44	98.52	0	0.00	0.00	3.74
Year 5	LCS16	95	87.61	4.74	82.87	0	0.00	0.00	4.45
2 years	LCS12	335	516.26	30.64	485.62	1	0.21	0.01	1.15
	LCS16	276	453.59	18.30	435.29	3	0.69	0.14	2.01
3 years	LCS12	335	698.48	38.61	659.87	1	0.15	0.00	0.84
	LCS16	276	627.24	22.16	605.08	4	0.66	0.18	1.69
4 years	LCS16	276	730.20	26.60	703.60	4	0.57	0.15	1.46
5 years	LCS16	276	817.80	31.34	786.47	4	0.51	0.14	1.30

Table 37. Contraceptive efficacy by BMI in the pooled studies (FAS): BMI < 30 kg/m²

Time	Treatment	Number of subjects	Total exposure [WY]	Excluded exposure [WY]	Relevant exposure [WY]	Number of pregnancies	Pearl Index	Lower 95% CIL	Upper 95% CIL
Overall	LCS12	3222	6649.81	253.77	6396.04	25	0.39	0.25	0.58
	LCS16	1417	4392.35	147.62	4244.73	14	0.33	0.18	0.55
Year 1	LCS12	3222	2913.40	159.48	2753.91	13	0.47	0.25	0.81
	LCS16	1417	1299.08	52.72	1246.37	2	0.16	0.02	0.58
Year 2	LCS12	2475	2013.83	41.71	1972.12	7	0.35	0.14	0.73
	LCS16	1192	1094.11	32.80	1061.31	5	0.47	0.15	1.10
Year 3	LCS12	1855	1704.37	47.09	1657.28	4	0.24	0.07	0.62
	LCS16	1008	927.88	27.19	900.68	4	0.44	0.12	1.14
Year 4	LCS16	731	575.22	14.45	560.77	1	0.18	0.00	0.99
Year 5	LCS16	539	491.93	18.42	473.51	2	0.42	0.05	1.53
2 years	LCS12	3222	4927.22	201.19	4726.03	20	0.42	0.26	0.65
	LCS16	1417	2393.19	85.52	2307.68	7	0.30	0.12	0.62
3 years	LCS12	3222	6631.60	248.28	6383.32	24	0.38	0.24	0.56
	LCS16	1417	3321.07	112.71	3208.36	11	0.34	0.17	0.61
4 years	LCS16	1417	3896.30	127.17	3769.13	12	0.32	0.16	0.56
5 years	LCS16	1417	4388.23	145.59	4242.64	14	0.33	0.18	0.55

10.2.2. Question 2

'Please state whether Jaydess will be marketed together with Kyleena, in Australia? If so, what principles are to be taken to prevent medication errors? This is considered relevant because the two products have different duration of contraception as the indication'.

10.2.2.1. Sponsor's response

There are no plans to market Jaydess in Australia, therefore Jaydess and Kyleena will not be marketed at the same time.

10.2.2.2. Evaluator's comment

The sponsor's response is acceptable.

10.2.3. Question 3

'Adverse effects included 'Table 4' that refers to bleeding patterns at 90 days to 5 years. The types of abnormalities discussed are amenorrhoea, infrequent bleeding, frequent bleeding and prolonged bleeding. Clearly this should only include the pivotal study and its extension to 5 years. The cross reference in the submission does not appear to relate to the findings of this study rather discusses the pooled data which is not a factual representation as the second study does not extend to 5 years. Please provide the results for the bleeding abnormalities that relate to the pivotal study and its extension arm. Please also provide the cross reference for these findings'.

10.2.3.1. Sponsor's response

Uterine bleeding is part of the safety analysis of the product and as for all other safety parameters the data is presented based on the pooled data from both the Phase II and Phase III studies. The evaluation of uterine bleeding, based on the pooled data across the pivotal LCS16 efficacy study and Phase II study, was considered representative for the first 3 years, and for the last 2 years, the data is based on the extension part of the pivotal study only. It should be noted that in the cross reference [not included here] the number of patients at each reference period (RP) represents only those patients who were still on treatment during that RP (N = number of women with valid reference period, n = number of women with event). Individual study findings are presented [not included here].

The table below presents the bleeding pattern data based only on the pivotal study, Report PH-37274. As can be seen from the updated table (see Table 38 below), there are only very minor differences in the frequencies of different bleeding patterns, whether the patterns are presented based on the pivotal study only, or based on the pooled data, as in the initial PI submitted.

Table 38. Bleeding patterns by 90 day reference period (pivotal study only)

	First 90 days (%)	Second 90 days (%)	End of Year 1 (%)	End of Year 3 (%)	End of Year 5 (%)
Amenorrhoea	< 1	5	13	20	23
Infrequent bleeding	10	21	27	26	26
Frequent bleeding	25	10	4	2	2
Prolonged bleeding*	57	14	6	2	1

*Subjects with prolonged bleeding may also be included in one of the other categories (excl. amenorrhea).

As part of the safety data, the sponsor proposes to present the bleeding profiles based on the pooled data rather than using the pivotal study only and therefore keep this table as per the initial PI submitted.

10.2.3.2. Evaluator's response

The sponsor's response is acceptable. The bleeding pattern data in the table of the proposed PI is based on pooled data provided. There are only a few small differences in the frequencies of the various bleeding patterns in the pivotal study shown above versus the pooled analysis provided in the PI, which is not unexpected given the pooled analysis is driven mainly by the pivotal study.

10.2.4. Question 4

'What is the evidence behind the concerns about Kyleena and use in congenital or valvular heart disease?'

10.2.4.1. Sponsor's response

There is no evidence from clinical trials with LCS16 that its use in women with congenital or valvular heart disease would adversely affect health of these women. The proposed precautionary statement is based on the current recommendations from available guidelines for intrauterine device (IUD) use in women with such conditions.

Congenital and acquired valvular heart disease and other congenital heart disease are the most common underlying cardiac conditions predisposing to infective endocarditis (IE).[5]

Cardiac conditions associated with the highest risk of adverse outcome from IE include the following (according to American Heart Association (AHA))[6]:

- Prosthetic cardiac valve or prosthetic material used for cardiac valve repair
- Previous IE
- Congenital heart disease (CHD) if referring to:
  - Unrepaired cyanotic CHD, including palliative shunts and conduits

[5] Cahill, T.J. and B.D. Prendergast, Infective endocarditis. Lancet, 2015.
[6] Wilson, W., et al., Prevention of infective endocarditis: guidelines from the American Heart Association: a guideline from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee, Council on Cardiovascular Disease in the Young, and the Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and the Quality of Care and Outcomes Research Interdisciplinary Working Group. Circulation, 2007. 116(15): p. 1736-54.

- Completely repaired CHD with prosthetic material or device whether placed by surgery or catheter intervention, during the first 6 months after procedure
- Repaired CHD with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device (which inhibit endothelialisation)

· Cardiac transplant recipient with cardiac valvulopathy.

According to previous guidelines, antibiotic prophylaxis was recommended for invasive genitourinary procedures including contraceptive procedures as it was considered that these may theoretically increase the risk of infective endocarditis. This is no longer recommended due to lack of evidence that such prophylaxis affects rates of infective endocarditis.[7]

The overview of recommendations from the available guidelines on endocarditis prophylaxis in genitourinary (GU) procedures as well as on IUD use in women with congenital or valvular heart disease is summarised in Tables 39 and 40 below.

Guidelines on endocarditis prophylaxis

Data on the risk of IE associated with a genitourinary tract procedure are limited, and no published data demonstrate a conclusive link between procedures of the genitourinary tract (GU procedures) and IE. The high prevalence of resistant strains of enterococci to penicillins, vancomycin and aminoglycosides (previously recommended treatment regimens), adds further doubt about the efficacy of prophylactic therapy for GU procedures.[6] Accordingly, antibiotic prophylaxis is not recommended for GU procedures (in absence of infection) by any of the pertinent current guidelines on antibiotic therapy for IE prevention. IUD insertion falls under GU procedures. While not specifically mentioned in the most current guidelines, it is worth noting that insertion or removal of intrauterine devices was specifically listed among the GU procedures for which endocarditis prophylaxis was not recommended already in the previous version of AHA recommendations published 1997.[8]

[7] Faculty of Sexual and Reproductive Healthcare Clinical Effectiveness Unit. FSRH Clinical Guidance: Contraceptive Choices for Women with Cardiac Disease; FRSH, Royal College of Obstetricians and Gynaecologists. June 2014.
[8] Dajani A et al. American Heart Association: Prevention of Bacterial Endocarditis Recommendations by the American Heart Association; Circulation. 1997;96:358-366

Table 39. Current guidelines on endocarditis prophylaxis

Guideline	Recommends AP for IE in	Recommendations on GU procedures	IUD insertion addressed?
AHA 2007[7]	Patients at highest risk* undergoing dental procedures Patient undergoing respiratory tract procedures with incision or biopsy Patients undergoing GI or GU tract procedures at sites with infection	No AP unless procedures at site with infection or to prevent wound infection/sepsis. No (longer) AP in women with vaginal delivery or hysterectomy	Not specifically addressed**
NICE 2008/2015[10]	Patients at risk with infection/undergoing intervention at site with (suspected) infection	No AP (only for procedures at site with (suspected) infection)	Not specifically addressed
ESC 2009/2015[11, 12]	Patients at highest risk* undergoing dental procedures	No AP unless established infection or to prevent wound infection/sepsis, in particular no AP for vaginal delivery or C-section	"Use of IUD considered acceptable", Reference to ESC guideline on CV disease during pregnancy (2011): "Antibiotic prophylaxis is not recommended at the time of insertion or removal since the risk of pelvic infection is not increased."
ACOG 2008/2009 [13, 14] and SCOG (Canada, 2012, [15])	N/A (aligned with AHA)	Aligned with AHA	No antibiotic prophylaxis for IUD insertion in general

* Highest risk: Prosthetic cardiac valve or prosthetic material used for cardiac valve repair; previous IE, congenital heart disease (CHD) if referring to unrepaired cyanotic CHD, including palliative shunts and conduits, completely repaired CHD with prosthetic material or device, during the first 6 months after procedure, repaired CHD with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device (which inhibit endothelialisation); cardiac transplant recipient with cardiac valvulopathy.
** Insertion or removal of intrauterine devices was already among the procedures for which endocarditis prophylaxis was not recommended in the 1997 AHA recommendations. ACOG American College of Obstetricians and Gynecologists, AHA American Heart Association, AP antibiotic prophylaxis, CV cardiovascular, ESC European Society of Cardiology, GI gastrointestinal, GU genito-urinary, NICE National Institute for Health and Care Excellence.

Medical Eligibility Criteria for Contraceptive Use (MEC)

The majority of guidelines on contraceptive use, that is, medical eligibility criteria (MEC) published by national and international societies have adopted the recommendations from antibiotic prophylaxis guidelines and do not/no longer recommend prophylactic antibiotics to prevent endocarditis (see Table 40 below). The only exception is the WHO MEC (2015), who advises to use antibiotic prophylaxis for insertion. This recommendation has remained largely unchanged since the first edition of the WHO MEC dating back to 1996.

Table 40. Medical Eligibility Criteria for Contraceptive Use (MEC) guidelines for antibiotic prophylaxis of endocarditis

MEC	Condition	Category for IUD use	Antibiotic prophylaxis addressed?	Other comments
US MEC 2016 [18]	Valvular heart disease: Uncomplicated Complicated*	 1 1	"According to the American Heart Association, administration of prophylactic antibiotics solely to prevent endocarditis is not recommended for patients who undergo genitourinary tract procedures, including insertion or removal of IUDs"	No direct evidence exists on the safety of IUDs among women with peripartum cardiomyopathy. Limited indirect evidence from noncomparative studies did not demonstrate any cases of arrhythmia or infective endocarditis in women with cardiac disease who used IUDs. Separate category for women with peripartum myocardiopathy (category 2), comment: IUD insertion might induce cardiac arrhythmias in healthy women; women with peripartum cardiomyopathy have a high incidence of cardiac arrhythmias.
UK MEC 2016 [19]	Valvular and congenital heart disease: Uncomplicated Complicated*	 1 2	"Prophylaxis against bacterial endocarditis is no longer indicated for women with artificial heart valves or previous endocarditis when inserting or removing IUC. However, this does not necessarily mean that there is no risk"	Congenital heart disease including Aortic stenosis; Atrial septal defects; Atrio-ventricular septal defect; Cardiomyopathy (hypertrophic or dilated); Coarctation of the Aorta; Complex Transposition of the Great Arteries; Ebstein's Anomaly; Eisenmenger Syndrome; Patent Ductus Arteriosus; Pulmonary Atresia; Pulmonary Stenosis; Tetralogy of Fallot; Total Anomalous Pulmonary Venous Connection; Tricuspid Atresia; Truncus Arteriosus; Ventricular Septal Defect
WHO MEC 2015 [16]	Valvular heart disease: Uncomplicated Complicated*	 1 2	"Clarification: Prophylactic antibiotics to prevent endocarditis are advised for insertion."	
FSRH guidance/ women with cardiac disease 2014 [8]	See UK MEC	See UK MEC	"Prophylactic antibiotics are not routinely required for the insertion or removal of intrauterine contraception in women with an increased risk of infective endocarditis."	"Vasovagal reactions may occur as a result of cervical stimulation during insertion or removal of intrauterine methods…the decision to use intrauterine contraception should involve a cardiologist….The intrauterine method should be fitted in a hospital setting if a vasovagal reaction presents a particularly high risk…."

* pulmonary hypertension, (risk for) atrial fibrillation, history of subacute bacterial endocarditis FSRH Faculty of Sexual and Reproductive Healthcare (UK).

Based on the above, the sponsor considers the current wording of the precaution to be adequate.

10.2.4.2. Evaluator's comment

The sponsor's response is acceptable. The proposed precautionary statement 'Heart Disease: Kyleena should be used with caution in women who have congenital heart disease or valvular heart disease and who are at risk of infective endocarditis' is contained in the current Jaydess PI.[3] There is no precautionary statement regarding heart disease in the US Skyla product label (US trade name for LNG12, that is, Jaydess) or UK SPC for Jaydess.[9,10] It is noted the current Australian Mirena PI contains the additional statement 'antibiotic prophylaxis should be

[9] US FDA Product label for Skyla.
[10] UK MHRA SPC for Jaydess.

administered to these patients when inserting or removing Mirena'.[2] The US product label for Mirena did contain information regarding use of antibiotics in patients with known congenital heart disease up to 2013, although this information is not present in the current US Mirena product label (dated 2015).[11,12] There is no precautionary information regarding valvular or congenital heart disease in the UK SPC for Mirena.[13]

10.2.5. Question 5

'Is there any evidence that the low systemic levels of progesterone associated with the use of Kyleena will cause problems with glucose metabolism?'

10.2.5.1. Sponsor's response

Study 310442 where haemoglobin A1c (HbA1c) was measured to assess carbohydrate metabolism at screening and end of study. The values are displayed in [table not included] of the Report PH-37274. Mean changes from baseline to end of study were small. The proportion of women with high HbA1c values did not change much from screening to end of study and were 1.3% at screening and 1.9% at end of study [table not included]. Transitions from Baseline with respect to reference ranges are displayed in [table not included]. A subject listing of HbA1c values at end of study can be found in the [appendix not included].

In addition, an overview of recommendations for LNG IUS use in women with diabetes from the available guidelines is presented in Table 41, below.

Table 41. Recommendations of LNG IUS use in diabetes

MEC	Condition	Category for LNG-IUS use	Other comments
US MEC 2016 [18]	Diabetes: a) History of gestational disease b) Non-vascular disease • Non-insulin-dependent • Insulin-dependent c) nephropathy/retinopathy/neuropathy d) other vascular disease or diabetes >20 years duration	1 2 2 2 2	
UK MEC 2016 [19]	Diabetes: a) History of gestational disease b) Non-vascular disease • Non-insulin-dependent • Insulin-dependent c) nephropathy/retinopathy/neuropathy d) other vascular disease	1 2 2 2 2	Limited evidence on the use of the LNG-IUS among women with insulin-dependent or non-insulin-dependent diabetes suggests that these methods have little effect on short- or long-term diabetes control (e.g. glycosylated hemoglobin levels), hemostatic markers or lipid profile.
WHO MEC 2015 [16]	Diabetes: a) History of gestational disease b) Non-vascular disease • Non-insulin-dependent • Insulin-dependent c) nephropathy/retinopathy/neuropathy d) other vascular disease or diabetes >20 years duration	1 2 2 2 2	Limited evidence on the use of the LNG-IUS among women with insulin-dependent or non-insulin-dependent diabetes suggests that these methods have little effect on short- or long-term diabetes control (e.g. HbA1c levels), hemostatic markers or lipid profile.

[11] US FDA Product Label for Mirena (2013)
[12] US FDA Product Label for Mirena (2015)
[13] UK MHRA SPC for Mirena

In summary, the recommendation given in the PI is in line with the recommendations given in the available guidelines. Therefore, in the sponsor's opinion, no changes to the PI are deemed necessary.

10.2.5.2. Evaluator's response

The sponsor's response is considered acceptable. The proposed Kyleena PI contains the identical precautionary text re: diabetes as the Mirena and Jaydess PI documents.[2,3] This information is also contained in the UK Jaydess SPC.[10]

10.2.6. Question 6

'Is it safe for women with a Kyleena IUD to undergo an MRI? What is the experience with similar products? Does there need to be a stronger warning against this?'

10.2.6.1. Sponsor's response

Yes, similar to Jaydess, Kyleena is MR conditional. Non-clinical testing of another LNG IUS (Jaydess) which has the same size silver ring and T-body has demonstrated that a patient can be scanned safely after placement of Kyleena under the conditions mentioned in the PI under 'Magnetic Resonance Imaging (MRI)'. Therefore, a stronger warning against MRI in Kyleena users is not warranted.

For TGA's reference, please find the report to support the inclusion of the precautionary statement [not included here]. The testing used is in accordance with the ASTM International recommendations and is generally accepted by the US FDA and is in line with the current FDA Guidance related to MR safety evaluation. The testing specifically evaluated magnetic field interactions, MRI related heating and artefact testing.

10.2.6.2. Evaluator's response

The Royal Australian and New Zealand College of Radiologists(RANZCR) MRI Safety Guidelines document categorises MR Compatibility Status as MR safe, MR conditional or MR unsafe as per ASTM (American Society for Testing and Materials) International definitions, noting the FDA requires product information labelling for all implants to have MR safety information available.[14] Jaydess is classified as MR conditional in the current Australian PI with the information provided consistent with the information in the US product label for Skyla.[3]

The RANZCR Guidelines define MR Conditional as: '*Has been demonstrated to pose no known hazards in a specified MR environment with specified conditions of use. Field conditions that define the specified MR environment include field strength, spatial gradient, dB/dt (time rate of change of the magnetic field) radio frequency (RF) fields, and specific absorption rate (SAR). Additional conditions, including specific configurations of the item, may be required*'.[14]

Use with MRI was raised in the Delegate's Overview for Jaydess and discussed at the ACPM Meeting 292. The following points are from the ACPM Ratified Minutes:

- There are limited safety data on the use of the silver collar in the proposed intrauterine device. The ACPM advised that lack of information provided to support the proposed PI statement on safety during an MRI should be included in a precaution. A discussion of the risks should be added to the education materials.
- The CMI should contain a warning on using JAYDESS in MRIs and a discussion of procedures for disposal in case of expulsion.
- The ACPM advised that the conditions of registration should include the following:

[14] The Royal Australian and New Zealand College of Radiologists Policy Library RANZCR MRI Safety Guidelines Version; April 2007.

- Subject to satisfactory negotiation of the Risk Management Plan most recently approved by the TGA, including provision of physician and consumer educational materials to the TGA. The need for notifying imaging staff concerning the silver collar before MRI procedures should be reflected in these documents.

The text in the Jaydess PI and CMI regarding MRI was finalised during post-ACPM PI negotiations.

10.2.7. Question 7

'Please comment on the risk of PID with Kyleena compared to the background rate of PID in sexually active women of this age without an IUD'.

10.2.7.1. Sponsor's response

Background incidence/prevalence

The background incidence for pelvic inflammatory disease (PID) is difficult to estimate. Diagnostic criteria for this disease entity differ between publications and studies.

Furthermore, the difficulty is augmented by an unknown number of silent PIDs which are not even noticed by the women affected.[15]

According to textbook knowledge one of 100 women in the age between 15 and 39 years develops an upper genital tract infection.[16]

In the US, the background incidence is cited as 15 to 20/1000 woman-years in age groups under 30, and about 8/1000 woman-years in the age group 30 to 40 (including ambulatory visits, and hospitalisations for PID during 1995 to 2001).[17] Overall, the rate of PID is declining.[18]

Clinical studies

In the clinical studies with LCS16, PID as diagnosed by the investigator was reported in 9 of 1697 women (1 woman in the Phase II study and 8 women in the pivotal LCS16 efficacy study), which is similar to the incidence observed with other LNG IUSs including Jaydess/LCS12. Most of the reported PIDs were moderate to severe in intensity, related to study drug, occurred in parous women, and occurred during Year 1 of the study, which is consistent with the published data on copper IUDs: PID associated with IUD insertion is confined to the first weeks after insertion.[19]

Table 42 below presents the crude incidence of PID in LCS12/Jaydess and LCS16 users by clinical study and Table 43 by duration of use (pooled).

[15] CDC, Centers for Disease Control and Prevention. Sexually Transmitted Disease Surveillance, 2006. Atlanta, GA: U.S. Department of Health and Human Services. November 2007.
[16] Eschenbach, D., Pelvic infections and sexually transmitted diseases. Danforth's obstetrics and gynecology, ed. J.R. Scott, et al. 2003. 9th ed. p. 581-603, Philadelphia (PA): Lippincott Williams & Williams.
[17] Sutton, M.Y., et al., Trends in pelvic inflammatory disease hospital discharges and ambulatory visits, United States, 1985-2001. Sex Transm Dis, 2005. 32(12): p. 778-84.
[18] CDC, Centers for Disease Control and Prevention. Sexually Transmitted Disease Surveillance, 2008. Atlanta, GA: U.S. Department of Health and Human Services. November 2009.
[19] Farley, T.M., et al., Intrauterine devices and pelvic inflammatory disease: an international perspective. Lancet, 1992. 339(8796): p. 785-8.

Table 42. Number of patients diagnosed with PID, as assessed by the investigator, by study

Study	LCS12	LCS16
310442/ Phase III	6[a]/1432 (0.4%)	6[a]/1452 (0.4%)
308901/ Phase II	0/240	1/245 (0.4%)
91775	6[b] /925	not applicable
13362	0/279	not applicable
13363 (12 month data)	1[c]/382	not applicable
14371 (12 month data)	0/304	not applicable
pooled	13/3562 (0.4%)	9/1697 (0.4%)

a) Numbers include one case reported as AE 'Salpingo-oophoritis' each; b) Includes one case reported as AE 'Salpingo-oophritis' and one report of AE 'endometritis'; c) Reported as AE 'salpingitis'.

Table 43. Number of patients diagnosed with PID, as assessed by the investigator, by duration of treatment (pooled)

Time of onset	LCS12	LCS16
Year 1	6 (66.6%)	8 (61.5%)
up to day 30	3 (33.3%)	2 (15.4%)
day 31- day 60	0	1 (7.7%)
day 61- day 90	1 (11.1%)	0
Q2 (day 91 - day 182)	1 (11.1%)	2 (15.4%)
Q3 (day 183 - day 274)	0	2 (15.4%)
Q4 (day 275 - day 365)	1 (11.1%)	1 (7.7%)
Year 2	0	1 (7.7%)
Year 3	1 (11.1%)	4 (30.8%)
Year 4	2 (22.2%)	0
Overall	**9 (100.0%)**	**13 (100.0%)**

Five of the 14 patients who had a PID diagnosis during the first year of treatment in either LCS dose were diagnosed during the first 30 days after insertion.

PID with other LNG IUS (Mirena)

In a large study randomising 2,758 women to Mirena (n = 1,821) or the copper IUD Nova T (n = 937), the 60 month gross removal rates (per 100) for PID were 2.2 in the Nova T and 0.8 in the LNG IUS group ($P < 0.05$). In the Mirena users, the incidence of PID was low regardless of age whereas in the Nova T group, there was a significantly ($P < 0.01$) increased PID rate compared to Mirena among the youngest women.[20]

Copper IUD related PID

Clinical trials and observational studies have established that the incidence of upper genital tract infections is considerably greater in the first month after insertion of a copper IUD than it is thereafter. Beyond the first month after insertion, the incidence of PIDs is low among women using IUDs and at a level that appears similar to that for women in general.[21] In the meta-analysis of WHO studies by Farley et al. (Copper IUDs), the incidence of PID was 9.7/1,000 women-years during the first month, later 1.4/1,000 woman years.[22]

[20] Toivonen, J., T. Luukkainen, and H. Allonen, Protective effect of intrauterine release of levonorgestrel on pelvic infection: three years' comparative experience of levonorgestrel- and copper-releasing intrauterine devices. Obstet Gynecol, 1991. 77(2): p. 261-4.
26. Andersson, K., V. Odlind, and G. Rybo, Levonorgestrel-releasing and copperreleasing
(Nova T) IUDs during five years of use: a randomized comparative trial. Contraception, 1994. 49(1): p. 56-72.
[21] Meirik, O., Intrauterine devices - upper and lower genital tract infections. Contraception, 2007. 75(6 Suppl): p. S41-7.
[22] Farley, T.M., et al., Intrauterine devices and pelvic inflammatory disease: an international perspective. Lancet, 1992. 339(8796): p. 785-8.
Toivonen, J., T. Luukkainen, and H. Allonen, Protective effect of intrauterine release of levonorgestrel on pelvic infection: three years' comparative experience of levonorgestrel- and copper-releasing intrauterine devices. Obstet

10.2.7.2. Evaluator's response

The sponsor's response is considered acceptable. The rate of PID does not seem greater than in the general population beyond the first month of insertion.

10.2.8. Question 8

'Please describe the evidence behind the following statement under Clinical Trials of the proposed PI: 'The use of Kyleena does not alter the course of the future fertility''.

10.2.8.1. Sponsor's response

The evidence regarding the topic 'Return to fertility' was detailed in the [data submitted] and is summarised as follows:

The use of LCS12 and LCS16 is not expected to alter the course of future fertility. In the studies conducted with LCS12 and LCS16, women who discontinue the method for wish of pregnancy were monitored for return to fertility (3 month follow-up in all women, and 12 month follow-up in women discontinuing the method for pregnancy wish):

- Phase II Study 308901: A total of 29 subjects discontinued the study due to a wish for pregnancy and 25 (86.2%) of these subjects (LCS16: 11, LCS12: 7 and Mirena: 11 women) had conceived within 12 months of end of study.
- Phase III Study 310442: A total of 99 women treated with LCS12 who discontinued the study because of a wish for pregnancy could be followed up at 12 months after discontinuation and were not using any contraception at that time. Of these 99 women, 76 or 76.8% became pregnant within 1 year of discontinuing treatment. Overall, 179 women discontinued the LCS16 treatment because of a wish for pregnancy at any time of the study, including the 5 year extension. Of these, follow up information is available for 163 women (91.1%), of which 116 women (71.2%) had become pregnant during the 12-month follow-up.
- The Asia Pacific Phase III Study 91775/Report PH-37275: Ten women who discontinued the study due to wish for pregnancy could be contacted at 12 months after discontinuation. Of these 10 women, 7 were pregnant.

Return to fertility with other LNG IUS

The use of Mirena does not alter the course of future fertility. Conception is possible in the first month after removal. The conception rate during the first year following removal observed in individual studies ranged from 79% to more than 90%.[23] Thus, a rate has been attained which corresponds to the normal range.

10.2.8.2. Evaluator's comment

The sponsor's response is acceptable. The pregnancy rates reported above are similar to 12 month pregnancy rates of approximately 80% reported in the literature (baseline prevalence

Gynecol, 1991.
77(2): p. 261-4.

[23] Allonen, H. and Y. Kulmala, Return to fertility after the removal of Nova-T or the levonorgestrel-IUD. Leiras Study report 1205, 1991. 1205: p. 1-24.
Andersson, K., I. Batar, and G. Rybo, Return to fertility after removal of a levonorgestrel-releasing intrauterine device and Nova-T. Contraception, 1992. 46(6):p. 575-84.
Belhadj, H., et al., Recovery of fertility after use of the levonorgestrel 20 mcg/d or Copper T 380 Ag intrauterine device. Contraception, 1986. 34(3): p. 261-7.
Sivin, I., et al., Rates and outcomes of planned pregnancy after use of Norplant capsules, Norplant II rods, or levonorgestrel-releasing or copper TCu 380Ag intrauterine contraceptive devices. Am J Obstet Gynecol, 1992. 166(4): p. 1208-13.
Mansour, D., et al., Fertility after discontinuation of contraception: a comprehensive review of the literature. Contraception, 2011. 84(5): p. 465-77.

of infertility, age and other factors affecting fertility rate notwithstanding).[24,25,26] Further, a review of 1-year pregnancy rates following cessation of contraception reported similar pregnancy rates following discontinuation of oral contraceptives and LNG-IUS (1 year pregnancy rates 80 to 95%).[26]

10.2.9. Question 9

'Please provide an update on overseas regulatory status for LCS16'.

10.2.9.1. Sponsor's response

Please find an update of the overseas regulatory status for LCS16.

10.2.9.2. Evaluator's response

The sponsor provided the following table.

Table 44. Foreign regulatory status (updated)

Country/region	Submission date	Status	Indications (approved or requested)	Other relevant information
Netherlands – decentralised procedure	20 November 2015	Submitted		
Sweden – decentralised procedure	20 November 2015	Submitted		The reference member state for the decentralised procedure is Sweden.
United Kingdom – decentralised procedure	20 November 2015	Submitted		
USA	18 November 2015	Submitted		
Canada	14 December 2015	Submitted		
Switzerland	11 December 2015	Submitted		
New Zealand	Q1 2017	Pending		
Singapore	N/A			

11. Second round benefit-risk assessment

11.1. Second round assessment of benefits

After consideration of the responses to clinical questions, the benefits of Kyleena in the proposed usage are unchanged from those identified in the first round assessment of benefits.

11.2. Second round assessment of risks

After consideration of the responses to clinical questions, the risks of Kyleena in the proposed usage are unchanged from those identified in the first round assessment of risks.

[24] Zinaman M et al. Estimates of human fertility and pregnancy loss. Fertil. Steril. 1996;65:503–509.
[25] Juul S et al. Regional differences in waiting time to pregnancy: pregnancy-based surveys from Denmark, France, Germany, Italy and Sweden. The European Infertility and Subfecundity Study Group. Hum. Reprod. 1999;14:1250–1254.
[26] Mansour D et al. Fertility after discontinuation of contraception: a comprehensive review of the literature. Contraception. 2011. 84(5):465-477.

- Although body weight can affect levonorgestrel clearance, the available data, albeit limited, for women with BMI ≥ 30 kg/m^2 do not suggest a clinically significant effect of body weight on contraceptive efficacy of LNG IUS. This is not unexpected given the predominant local effect of Kyleena.
- Use in MRI remains an unknown risk. Mirena does not contain metallic components and Jaydess (which does contain the silver ring) is not marketed in Australia. Appropriate information regarding this risk needs to be adequately communicated in the PI/CMI documents and patient card.
- Use in heart disease is an uncertain risk; the Sponsor is asked to clarify the discrepancy regarding the proposed text in Kyleena and that in the current Mirena PI, the latter recommending antibiotic prophylaxis when inserting or removing Mirena.

11.3. Second round assessment of benefit-risk balance

The benefit-risk balance of Kyleena, given the proposed usage, is favourable.

Contraceptive efficacy over 5 years with LCS16 has been demonstrated with an overall Pearl Index of 0.29 (95% CI: 016, 0.50). There was no trend observed with pregnancy rate over time. The cumulative failure rate at 5 years (1.4%) was similar to the cumulative failure rate at 3 years for the LCS16 arm (1.0%).

There were no new or unexpected safety findings. Ectopic pregnancy is a known safety issue with LNG IUS. The unadjusted 5 year Pearl Index for ectopic pregnancy for LCS16 in the pivotal study was 0.18 (95% CI: 0.08, 0.36), which is slightly higher than the overall incidence of ectopic pregnancy for Jaydess (0.11 per 100 WY), although lower than the rates in women not using any contraception (0.3 to 0.5 per 100 WY).[3] The increased likelihood of a pregnancy being ectopic if pregnancy occurs with Kyleena in situ is clearly documented in the proposed PI. Further, the known risks of pelvic infection, expulsion and perforation are well characterised in the proposed PI.

12. Second round recommendation regarding authorisation

Approval of the application to register the product Kyleena is recommended for the indication 'Contraception for up to 5 years' provided all chemistry and quality control issues are resolved.

13. References

Australian CMI for Mirena, Bayer Australia Ltd.

Australian PI Jaydess (TGA PI/CMI repository), Bayer Australia Ltd.

Australian PI Mirena, Bayer Australia Ltd.

Juul S et al. Regional differences in waiting time to pregnancy: pregnancy-based surveys from Denmark, France, Germany, Italy and Sweden. The European Infertility and Subfecundity Study Group. Hum. Reprod. 1999;14:1250–1254.

Mansour D et al. Fertility after discontinuation of contraception: a comprehensive review of the literature. Contraception. 2011. 84(5):465-477.

UK MHRA SPC for Jaydess, Bayer (UK) Plc.

UK MHRA SPC for Mirena, Bayer (UK) Plc.

The Royal Australian and New Zealand College of Radiologists Policy Library RANZCR MRI Safety Guidelines Version April 2007.

US FDA Product label for Mirena (2013).

US FDA Product label for Mirena (2015).

US FDA Product label for Skyla.

Zinaman M et al. Estimates of human fertility and pregnancy loss. Fertil. Steril. 1996;65:503–509.

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