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Department of Health

Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for ulipristal acetate

Proprietary Product Name: EllaOne

Sponsor: ERA Consulting (Australia) Pty Ltd

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List of abbreviations

Abbreviation	Meaning
AE	Adverse Event
ALT	Alanine aminotransferase
AST	Aspartate aminotrasferase
AUC	Area Under the Curve
AUC0-inf	Area Under the plasma concentration time Curve from time 0 to infinity
AUC0-t	Area Under the plasma concentration time Curve from time 0 to last observation
CL/F	Clearance divided by bioavailablity (plasma clearance of an orally administered dose)
Cmax	Maximum plasma concentration
CV	Coefficient of Variability
DAE	Adverse Event leading to Discontinuation
EC	Emergency Contraception
HCP	Health Care Professional
HSUP	High Sensitivity Urine Pregnancy test
ITT	Intention To Treat
IUD	Intra-Uterine Device
LH	Lutenising Hormone
MITT	modified Intention To Treat
PI	Product Information document
PD	Pharmacodynamics
PK	Pharmacokinetics
SAE	Serious Adverse Event
SD	Standard Deviation

Abbreviation	Meaning
SE	Standard Error
SPRM	Selective Progesterone Receptor Modulator
TEAE	Treatment Emergent Adverse Event
$t\frac{1}{2}$	Half-life
Tmax	Time to maximum plasma concentration
UPI	Un-Protected Intercourse

1. Clinical rationale

There is a clinical need for the availability of emergency contraception because of the health and social costs of unplanned pregnancy. Unplanned pregnancy may result from contraception failure or situations where intercourse is not anticipated or has been coerced. Abortion is a less acceptable alternative to emergency contraception. High dose oestrogen progestin regimens, and more recently levonorgestrel, have been previously used as emergency contraception. However, with levonorgestrel reported pregnancy rates rise from approximately 1.5 to 2.6%, respectively, for intake 0 to 24 h as compared to intake 48 to 72 h after intercourse. Hence, ulipristal offers the potential for emergency contraception that can be taken within 5 days of UPI.

2. Contents of the clinical dossier

2.1. Scope of the clinical dossier

The submission contained the following clinical information:

- 19 clinical pharmacology studies, including 14 that provided pharmacokinetic data and 6 that provided pharmacodynamic data;
- No population pharmacokinetic analyses;
- One pivotal efficacy/safety study;
- Two dose finding studies;
- Two other efficacy/safety studies;
- Four pooled analyses, seven periodic safety update reports (PSURs), and one postmarketing study.

2.2. Paediatric data

The submission included data for females aged 13 years and over. The sponsor has an approved paediatric investigation plan (PIP) that includes adolescent girls aged 12 to 17 years. The sponsor has a waiver for children aged ≤12 years because pre menarchic girls are not considered to be at risk of pregnancy.

2.3. Good clinical practice

The clinical studies were stated, and appeared, to have been conducted according to Good Clinical Practice.

3. Pharmacokinetics

3.1. Studies providing pharmacokinetic data

Table 1 shows the studies relating to each pharmacokinetic topic and the location of each study summary.

Table 1: Submitted pharmacokinetic studies.

PK topic	Subtopic	Study ID
PK in healthy adults	General PK - Single dose	Pasarro <i>et al</i> 2003 Study HRA2914-504 Study HRA2914-553 Study PGL09-023
	- Multi-dose	
	Bioequivalence - Single dose	Study 111014-001 Study 02-CH-0219 Study HRA2914-011
	Food effect	Study HRA2914-008
PK in special populations	Target population - Single dose	none
	Hepatic impairment	None
	Renal impairment	None
	Neonates/infants/children/adolescents	None
	Elderly	None
Genetic/gender-related PK	Lactating females	Study HRA2914-514
PK interactions	Esomeprazole	Study HRA2914-546
	Ketoconazole	Study HRA2914-547
	Fexofenadine	Study HRA2914-548
	Erythromycin	Study HRA2914-549
	Rifampicin	Study HRA2914-551

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

3.2. Summary of pharmacokinetics

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

3.2.1. Physicochemical characteristics of the active substance

The following information is derived from the sponsor's PI. Ulipristal acetate is a white to yellowish crystalline powder. It is freely soluble in methylene chloride, soluble in methanol, acetone and ethanol and insoluble in water.

3.2.2. Pharmacokinetics in healthy subjects

3.2.2.1. Absorption

3.2.2.1.1. Sites and mechanisms of absorption

In Study 111014-001, mean (CV%) Cmax following a 30 mg oral tablet was 223 (36.7%) ng/mL, there was no absorption time lag and median (range) Tmax was 0.500 (0.50 to 1.00) hours.

In Study HRA2914-504, for a 30 mg oral dose, mean (SD) CL/F was 76.8 (64.0) L/h, Cmax was 176 (88.9) ng/mL, AUC0-inf was 556 (260) h·ng/mL and t_{1/2} was 32.4 (6.33) hours. Median (range) Tmax was 0.88 (0.50 to 2.00) hours. The plasma concentration time profile was consistent with a two compartment model.

3.2.2.2. Bioavailability

3.2.2.2.1. Absolute bioavailability

In Study 111014-001, mean (SD) absolute oral bioavailability was 27.46 (4.97) %.

3.2.2.2.2. Bioequivalence of clinical trial and market formulations

In Study 2914-011, ulipristal 30 mg tablets manufactured at LEON Farma and at Cardinal Health France were found to be bioequivalent.

3.2.2.2.3. *Bioequivalence of different dosage forms and strengths*

In Study 02-CH-0219, the bioavailability of a 10 mg micronised tablet formulation was similar to that for a micronised capsule formulation, but greater than for a crystalline capsule formulation. AUC was increased by approximately 40% for both ulipristal and its major metabolite in the micronised tablet formulation relative to the crystalline capsule formulation.

3.2.2.2.4. *Influence of food*

Food decreased the rate of absorption of ulipristal, but increased bioavailability. In Study 2914-008, following a high fat breakfast, compared to fasted, Cmax was decreased by 44% and Tmax was increased by 1.5 hours for both ulipristal and its major metabolite (3877A). However, AUC increased by approximately 25%.

3.2.2.2.5. *Dose proportionality*

In Pasarro et al 2003, the PK for ulipristal were not dose-proportional in the dose range 1 mg to 200 mg, with a relative decrease in AUC and Cmax with increasing dose.

In Study PGL09-023, the PK for ulipristal were not dose proportional in the dose range 10 mg to 50 mg. Dose-normalized AUC were 1.4 and 1.1 fold higher with the 20 mg and 50 mg dose, respectively, compared to the dose of 10 mg.

3.2.2.2.6. *Bioavailability during multiple-dosing*

In Study PGL09-023 with multiple daily dosing over 10 days, and in the dose range 10 mg to 50 mg there was no unpredictable accumulation of ulipristal and no indication of changes in metabolism over time. Over the 10 day period there were also no changes in the metabolism of PGL4002.

3.2.2.3. *Distribution*

3.2.2.3.1. *Volume of distribution*

In Study 111014-001, mean (CV%) volume of distribution was 644.000 L (32.9%).

3.2.2.3.2. *Plasma protein binding*

Although there were no clinical data with regard to protein binding, the Non-Clinical overview states: "In humans, ulipristal acetate is highly bound in plasma (94.1% to plasma proteins), with a free fraction just above 1%. In human plasma, ulipristal acetate is mainly bound to α -acid glycoprotein, human serum albumin, high density lipoprotein and low density lipoprotein. The total protein binding remained constant over the concentration range tested despite a saturable binding to α -acid glycoprotein (HRA2914-427)."

3.2.2.4. *Metabolism*

3.2.2.4.1. *Sites of metabolism and mechanisms / enzyme systems involved*

Ulipristal acetate is predominantly metabolised by CYP3A4.

3.2.2.5. *Non-renal clearance*

In Study HRA2914-553, following a single oral dose of 14C-Ulipristal 20 mg 6% of radioactivity was recovered in urine within 48 hours of dosing. Hence ulipristal clearance is predominantly non-renal. There was 72% of administered radioactivity recovered in faeces over 264 hours.

3.2.2.5.1. *Metabolites identified in humans*

3.2.2.5.1.1. *Active metabolites*

Ulipristal acetate main active metabolite is monodemethyl-ulipristal acetate.

3.2.2.5.1.2. Other metabolites

In Study HRA2914-553, following a single oral dose of 14C-Ulipristal 20 mg approximately 80% of the administered radioactivity was recovered. There was 72% of administered radioactivity recovered in faeces over 264 hours, and 6% of radioactivity was recovered in urine within 48 hours of dosing. The principal metabolite was PGL4002 and systemic exposure was 33% of the parent drug. Total radioactivity in plasma and whole blood was more slowly eliminated than ulipristal and PGL4002, resulting in mean elimination half-lives of 120 and 260 hours, respectively. This prolonged elimination suggests the presence of unidentified metabolites that are slowly cleared from the systemic circulation.

3.2.2.5.2. *Pharmacokinetics of metabolites*

In Study 2914-011, the half life of 11-demethyl-ulipristal acetate was around 41 hours. Tmax was 1 hour, indicating rapid biotransformation of ulipristal acetate to its major metabolite.

3.2.2.6. *Excretion*

3.2.2.6.1. *Routes and mechanisms of excretion*

In Study 111014-001, mean (CV%) clearance of ulipristal was 10.300 L/hour (26.1%).

In Study 111014-001, mean (CV%) t_{1/2} was approximately 43.280 (30.4) hours.

3.2.2.6.2. *Mass balance studies*

As per above.

3.2.2.6.3. *Renal clearance*

Renal clearance of unchanged ulipristal is minimal.

3.2.3. **Pharmacokinetics in the target population**

PK studies were not conducted in the target population. However, the target population is healthy females and this would be similar to the volunteer populations used in the PK studies.

3.2.4. **Pharmacokinetics in other special populations**

3.2.4.1. *Pharmacokinetics in subjects with impaired hepatic function*

No data.

3.2.4.2. *Pharmacokinetics in subjects with impaired renal function*

No data.

3.2.4.3. *Pharmacokinetics according to age*

No data.

3.2.4.4. *Pharmacokinetics related to genetic factors*

No data.

3.2.4.5. *Pharmacokinetics in lactating women*

In Study HRA2914-514, the excretion of ulipristal into breast milk was investigated. Following a 30 mg tablet of ulipristal, mean (SD) plasma C_{max} was 259.82 (155.73) ng/mL, AUC_{0-t} was 813.71 (292.61) h•ng/mL and median (range) Tmax was 0.88 (0.5 to 2.0) hours. Mean (SD) breast milk C_{max} was 92.08 (49.72) ng/mL, AUC_{0-t} was 565.25 (292.61) h•ng/mL and median (range) Tmax was 0.88 (0.5 to 2.0) hours. Over the first 24 hours post dose an infant would be exposed to 0.04% of the dose, and over the second 24 hours post-dose a further 0.01%.

3.2.5. Pharmacokinetic interactions

3.2.5.1. Pharmacokinetic interactions demonstrated in human studies

Esomeprazole decreases the rate of absorption of ulipristal but does not significantly affect overall exposure, and does not affect half-life. In Study HRA2914-546, comedication with esomeprazole increased Tmax from 0.75 hours to 1 hour, and decreased Cmax from 61.0 ng/mL to 21.2 ng/mL. However, there was bioequivalence as evaluated by AUC. The mean (90% CI) ratio for AUC0-t, ulipristal + esomeprazole / ulipristal, was 1.152 (1.0151 to 1.3071). The half-life of ulipristal administered alone was 43.02 hours, and with esomeprazole was 45.55 hours.

Co-administration with ketoconazole doubled Cmax and increased AUC by approximately 500%. In Study HRA2914-547, the mean ratio (90% CI), ulipristal + ketoconazole / ulipristal was 1.96 (1.71 to 2.25) for Cmax and 5.86 (5.08 to 6.77) for AUC0-inf. CL/F for ulipristal decreased from 58.4 L/hour to 10.0 L/hour. For the primary metabolite, PGL4002, the mean ratio (90% CI), ulipristal + ketoconazole / ulipristal was 0.53 (0.47 to 0.60) for Cmax and 2.41 (2.13 to 2.72) for AUC0-inf. For PGL4002 CL/F decreased from 169.5 L/hour to 70.2 L/hour.

In Study HRA2914-548, there was no significant effect of ulipristal on the PK of fexofenadine, a p-glycoprotein substrate. The mean ratio (90% CI), fexofenadine + ulipristal / fexofenadine, for AUC0-inf was 0.97 (0.86 to 1.11) and for Cmax was 0.91 (0.77 to 1.06).

Erythromycin resulted in increased bioavailability of ulipristal and increased half-life for PGL4002. In Study HRA2914-549, concomitant erythromycin resulted in an 18.17% increase in Cmax and 191.86% increase in AUC0-inf for ulipristal. However ulipristal half-life was unchanged (approximately 35 hours). For PGL4002, with concomitant erythromycin, Cmax was decreased by 52.04%, AUC0-inf increased by 52.81% and half-life increased from 23.89 hours to 47.69 hours.

In Study HRA2914-551, co-administration of rifampicin decreased exposure to ulipristal by more than 90%. The AUC0-inf decreased from 673.1 h•ng/mL to 51.1 h•ng/mL and Cmax decreased from 250 ng/mL to 26.3 ng/mL. The half-life of ulipristal decreased from 34.83 h to 15.84 h. The AUC0-inf for monodemethylated UPA decreased by 93% from 255.4 h•ng/mL to 25.0 h•ng/mL.

3.2.5.2. Clinical implications of in vitro findings

Ulipristal appears to be metabolised primarily by CYP3A4. Hence induction of CYP3A4, for example co-administration of St John's Wort) may impair efficacy. Inhibition of CYP3A4 may result in an increased risk of adverse reaction.

3.3. Evaluator's conclusions on pharmacokinetics

The pharmacokinetic data presented in the submission are consistent with the PK properties stated in the proposed PI document. The pharmacokinetics of ulipristal have been adequately described for the population intended in the proposed indication, that is, women of childbearing potential. However, should ulipristal be proposed for use in other populations, such as the elderly, patients with impaired renal function or patients with impaired hepatic function, then further pharmacokinetic data should be provided.¹

¹ The sponsor notes this refers to a use in elderly women, which is not intended and would be off-label.

4. Pharmacodynamics

4.1. Studies providing pharmacodynamic data

Table 2 shows the studies relating to each pharmacodynamic topic and the location of each study summary.

Table 2: Submitted pharmacodynamic studies.

PD Topic	Subtopic	Study ID
Primary Pharmacology	Effect on luteolysis	Pasarro <i>et al</i> 2003
	Effect on foliculogenesis	Study HRA2914-505
	Follicle rupture	Study HRA2914-511
	Menstrual cycle	Study HRA2914-506
	Ovulation	Study HRA2914-510
		Study HRA2914-554

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

4.2. Summary of pharmacodynamics

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

4.2.1. Mechanism of action

Ulipristal acetate is a synthetic selective progesterone receptor modulator that acts via high-affinity binding to the human progesterone receptor.

4.2.2. Pharmacodynamic effects

4.2.2.1. Primary pharmacodynamic effects

In Pasarro *et al* 2003, at a dose of 200 mg all of six volunteers had early bleeding at the 200 mg dose level, and at the 50 mg and 100 mg dose levels approximately half of the subjects had early bleeding.

In Study HRA2914-505, there was a dose dependent increase in the time to follicular collapse following ulipristal in the dose range 10 mg to 100 mg, compared to placebo. There was an arrest in follicular growth at the 100 mg dose level, with dose dependent decrease in follicular growth at the 10 mg and 50 mg dose levels. Plasma oestradiol concentrations were suppressed at the 50 mg and 100 mg dose levels ($p < 0.001$). There was delayed endometrial maturation in two (16.7%) women in the placebo group, none in the 10 mg group, four (36.4%) in the 50 mg group and seven (70%) in the 100 mg group. There was a dose dependent increase in menstrual cycle length: mean (SE) 29 (1.3) days in the placebo group, 29 (1.0) days in the 10 mg, 33 (1.5) days in the 50 mg and 33 (1.4) days in the 100 mg. There was no difference between the groups in the length of the subsequent menstrual cycle.

In Study HRA2914-506, there were no significant differences in length of follicular or luteal phase, or overall length of menstrual cycle. There was a significant increase in delayed endometrial maturation in the ulipristal 50 mg and 100 mg groups when compared to the placebo and 10 mg groups: OR (95% CI) 4.2 (1.0 - 17.6); Fisher's exact test, $p = 0.05$. There was a significant reduction in endometrial thickness among those subjects receiving higher doses of ulipristal (50 or 100 mg) compared to those receiving placebo or 10 mg: mean (SD) high-dose: 9.3 (1.9) mm, low-dose: 11.0 (3.1) mm; $p=0.01$. Glandular progesterone receptor staining differed among treatment groups (Fisher's exact test; $p=0.02$) with those receiving higher ulipristal doses demonstrating greater staining as evidenced by immunohistochemistry.

In Study HRA2914-510, anovulation occurred in one (9.1%) subjects in the 2.5 mg group, nine (81.8%) in the 5 mg, eight (80%) in the 10 mg and none in the placebo. This was statistically significant for the 5 mg and 10 mg groups compared to placebo ($p < 0.001$). Estradiol, FSH and LH concentrations were in the normal range. There was no significant effect on follicular growth. Amenorrhea was achieved in 81.8% women in the 5 mg group and 90% women in 10 mg group by the third month of treatment, while only 18.2% women were amenorrheic in the 2.5 mg group and none were amenorrheic in the placebo group. No significant modification of the Insler score compared to baseline was observed in treated women, suggesting the absence of progestogenic effect of the compound on cervical glands. In the 10 mg group, 60% of subjects had atrophic endometrium.

In Study HRA2914-511, following a single dose of ulipristal 30 mg, when lead follicle reached 18 mm, there were the following findings:

- Follicle rupture inhibited in 15 (44%) of ulipristal treated cycles and none (0%) of placebo treated, $p = 0.0001$.
- When administered after the LH surge seven (36.8%) of ulipristal treated cycles had inhibition of follicle rupture, compared with none (0%) of the placebo, $p = 0.0082$.
- Mean (SD) time to follicular rupture was 6.03 (3.86) days in the ulipristal group and 2.41 (1.31) days in the placebo, $p < 0.0001$.
- Continued growth of the follicle occurred for 18 (75%) of the ulipristal treated and 6 (25%) of the placebo, $p = 0.0013$.
- Mean (SD) cycle length was 32.68 (3.75) days in the ulipristal group and 30.18 (4.11) days in the placebo, $p = 0.0024$.
- LH surge was detected in 26 (76.5%) of ulipristal treated cycles and 33 (97.1%) of placebo.
- There was no significant difference in mean LH concentrations between the treatment groups. However there was no other difference between the groups for indicators of ovulation.

In Study HRA2914-554, when comparing ulipristal dosing regimens of 30 mg weekly and 30 mg every 5 days:

- There was no significant difference between the treatment groups in risk of ovulation: occurrence of ovulation at least once during the 8 week treatment period was 11 (91.7%) for the weekly group and 8 (72.7%) for the every 5 days group
- Of the ovulatory cycles, only one in the weekly group was considered not to be at risk for pregnancy
- Luteinised, unruptured follicles occurred during the 8 week treatment period in 5 (41.7%) subjects in the weekly group and one (9.1%) in the every 5 days group
- Persistent follicles occurred in one subject in the weekly group and two in the every five days group
- Neither treatment regimen affected cervical mucous. LH, oestradiol and progesterone concentrations were within physiological ranges.

4.2.2.2. Secondary pharmacodynamic effects

Secondary pharmacodynamic effects were not studied.

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

Genetic, gender and age-related differences in pharmacodynamic response were not studied.

4.2.4. Pharmacodynamic interactions

Pharmacodynamic interactions were not studied.

4.3. Evaluator's conclusions on pharmacodynamics

The pharmacodynamic studies examined the ulipristal dose range from 10 to 200 mg as a single dose. There were dose dependent effects on follicular growth, follicular rupture, endometrial growth and cycle length. These effects were not significant at the 10 mg dose level. At the 30 mg dose level in Study HRA2914-511, following a single dose of ulipristal 30 mg, when lead follicle reached 18 mm, there were the following findings:

- Follicle rupture inhibited in 15 (44%) of ulipristal treated cycles and none (0%) of placebo treated, $p = 0.0001$;
- When administered after the LH surge, seven (36.8%) of ulipristal treated cycles had inhibition of follicle rupture, compared with none (0%) of the placebo, $p = 0.0082$;
- Mean (SD) time to follicular rupture was 6.03 (3.86) days in the ulipristal group and 2.41 (1.31) in the placebo, $p < 0.0001$;
- Continued growth of the follicle occurred for 18 (75%) of the ulipristal treated and 6 (25%) of the placebo, $p = 0.0013$;
- Mean (SD) cycle length was 32.68 (3.75) days in the ulipristal group and 30.18 (4.11) days in the placebo, $p = 0.0024$;
- LH surge was detected in 26 (76.5%) of ulipristal treated cycles and 33 (97.1%) of placebo. Ulipristal did not alter cervical mucous.

The pharmacodynamic characteristics of ulipristal have been adequately characterised for the proposed indication.

5. Dosage selection for the pivotal studies

5.1. Study HRA2914-507

Study HRA2914-507 was a multicentre, randomised, double blind, active controlled study to assess the efficacy, safety and tolerance of ulipristal in comparison with levonorgestrel for emergency contraception. The study was conducted at seven sites in the US from September 1999 to September 2001.

The inclusion criteria included:

- Menstruating women >18 years age
- Requested emergency contraception within 72 h (3 days) after unprotected coitus, as defined by lack of contraceptive use, or condom breakage (including condoms lubricated with spermicide) or other barrier contraceptive method failure;
- Reported that all acts of unprotected coitus during the enrolment cycle were within 72 h prior to enrolment;
- Women who were willing to abstain from further acts of UPI during the treatment cycle;
- Had a history of regular menstrual cycles (mean length of 24-42 days with intra individual variation of ± 5 days);
- Had ≥ 1 normal menstrual cycle (2 menses) post delivery or abortion;

- If subject had recently discontinued hormonal contraception, one normal menstrual cycle (2 menses) must have been completed before entry in the study;
- For women who had a recent history of Depo-Provera use, the most recent injection must have been at least 3 months before study entry and the subject must have had at least one normal menstrual cycle (2 menses).
- Was available for follow-up \geq 4 weeks.

The exclusion criteria included:

- Pregnant at screening or enrolment (positive high-sensitivity urine pregnancy test);
- Had been pregnant or breast feeding within the 2 months prior to screening and enrolment;
- Had used hormonal methods of contraception during the enrolment cycle or previous two cycles;
- Was an intrauterine device (IUD) user at the time of screening or enrolment;
- Had a Tubal ligation;
- Had a partner with a history of vasectomy;
- Was unsure about the date of the last menstrual period (+3 days);
- Had irregular menstrual cycles, as defined in the inclusion criteria;
- Had experienced nausea and vomiting within the 2 weeks prior to screening and enrolment;
- Had impaired hypothalamic-pituitary-adrenal reserve or had received oral glucocorticoid replacement therapy in the year prior to screening and enrolment; and
- Was not concurrently enrolled in any other investigational trial and agreed not to re-enrol in this study.

The study treatments were:

1. Ulipristal 50 mg unmicrosised in gelatin capsules
2. Levonorgestrel 0.75 mg, two doses taken up to 12 h apart

The treatments were self administered as a single dose up to 72 h after UPI.

The primary efficacy outcome measure was the rate of post treatment pregnancy. The secondary efficacy outcome measures were: the incidence of pregnancy in an efficacy evaluable population, the tolerability of ulipristal (as measured by the incidence of nausea and vomiting), and the effects of ulipristal on the menstrual cycle. The safety outcome measures were adverse events (AEs) and symptom diary.

A total of 1672 subjects were randomised: 832 to ulipristal and 840 to levonorgestrel. There were 792 subjects in the ulipristal group and 786 in the levonorgestrel that completed the study. The mean (SD) age was 24.4 (5.77) in the ulipristal group and 24.2 (5.59) in the levonorgestrel. The treatment groups were similar in demographic characteristics. The medical and gynaecological histories were similar for the two treatment groups.

There were 12 pregnancies in the ulipristal group and 14 in the levonorgestrel. The pregnancy rate (95% Confidence Interval [CI]) was 1.52 (0.785 to 2.632) % in the ulipristal group and 1.78 (0.977 to 2.970) % in the levonorgestrel. The mean (95% CI) difference in pregnancy rates, ulipristal – levonorgestrel was -0.27 (-1.992 to 1.420) %.

In the efficacy evaluable population, there were seven post treatment pregnancies in the ulipristal group and 13 in the levonorgestrel. The post treatment pregnancy rate (95% CI) was 0.91 (0.365 to 1.857) % in the ulipristal group and 1.68 (0.898 to 2.859) % in the

levonorgestrel. The mean (95% CI) difference in pregnancy rates, ulipristal – levonorgestrel was -0.78 (-2.407 to 0.773) %.

5.2. Study HRA2914-508

Study HRA2914-508 was a multicentre, randomised, active controlled study to assess the efficacy, safety and tolerance of two different doses of ulipristal for emergency contraception. The study was conducted at nine sites in the US from August 2001 to November 2003.

The inclusion and exclusion criteria were the same as for Study HRA2914-507.

The study treatments were:

1. Ulipristal 50 mg, unmicronised in gelatin capsule
2. Ulipristal 10 mg, micronised in gelatin capsule
3. Ulipristal 10 mg, unmicronised in gelatin capsule (discontinued arm)

The treatments were administered as a single dose up to 72 h after UPI. There was no placebo or other active comparator.

The primary efficacy outcome measure was pregnancy. Suspected pregnancy was initially detected by a urine pregnancy test, and if this was positive quantitative serum β -hCG (human chorionic gonadotropin) and ultrasound to determine gestational age. Tolerance was measured by comparing the incidence of vomiting and nausea using a daily diary. The safety outcome measures were AEs and concomitant medications.

A total of 1026 subjects were randomised to treatment: 413 to unmicronised 50 mg, 399 to micronised 10 mg and 214 to unmicronised 10 mg. There were 952 evaluable subjects: 384 in the unmicronised 50 mg group, 365 in the micronised 10 mg and 203 in the unmicronised 10 mg. The mean (SD) age was 24.4 (5.6) years and the treatment groups were similar in demographic characteristics.

There were five pregnancies in the ulipristal unmicronised 50 mg group and ten in the micronised 10 mg group. The pregnancy rate (95% CI) was 1.30 (0.423 to 3.016) % in the unmicronised 50 mg group and 2.74 (1.320 to 4.985) % in the micronised 10 mg. The mean (95% CI) difference in pregnancy rates, 10-50 mg, was 1.44 (-0.660 to 3.820) %. The expected number of pregnancies in each of the treatment groups was 21: hence the contraceptive effectiveness was 76.19% for the unmicronised 50 mg and 52.38 for the micronised 10 mg. There were ten pregnancies in the 203 subjects in the unmicronised 10 mg arm (discontinued arm).

5.3. Conclusions with regard to the dose finding studies

Study HRA2914-507 and Study HRA2914-508 were both conducted using dose levels other than that proposed for marketing. Up to 72 h after UPI, ulipristal 50 mg, unmicronised in gelatin capsules, as a single dose had comparable efficacy to levonorgestrel 0.75 mg, two doses taken up to 12 h apart. However, although ulipristal 10 mg, micronised, appeared to have lower efficacy than an unmicronised 50 mg dose, both were considered to be at least 50% effective. Although there was more nausea with the 10 mg micronised dose, indicating this AE did not appear to be dose related, the sponsor opted for a dose lower than the 50 mg level in further development.

6. Clinical efficacy

6.1. Emergency contraception

6.1.1. Pivotal efficacy studies

6.1.1.1. Study HRA2914-513

6.1.1.1.1. Study design, objectives, locations and dates

Study HRA2914-513 was a multicentre, single blind, randomised, two-arm, comparator controlled study to evaluate the observed pregnancy rate following ulipristal 30 mg within 72 hours of unprotected intercourse. The study also investigate efficacy up to 120 hours after UPI. The study was conducted by 17 investigators: 10 in UK/Ireland and 7 in the US from April 2007 to April 2009.

6.1.1.1.2. Inclusion and exclusion criteria

The inclusion criteria included:

- Women, 16 years of age or older in the UK (except Northern Ireland), 17 years or older in Northern Ireland (UK) and 18 years or older in Ireland and the US
- Had regular menstrual cycle (between 24 and 35 days) and intra-individual variations less than or equal to 5 days
- EC requested within 120 hours after UPI. UPI was defined by lack of contraceptive use, condom breakage (including condoms lubricated with spermicide) or other barrier contraceptive method failure
- No current use of hormonal contraception and at least one complete menstrual cycle (two menses) since hormonal contraception was stopped
- If there was a recent history of Depo Provera use, the most recent injection was to be at least 9 months before study entry and followed by at least one complete menstrual cycle (two menses)
- Willing not to use hormonal methods of contraception until study completion
- At least one complete menstrual cycle (two menses) post delivery, miscarriage or abortion
- Women who presented more than 72 hours after intercourse, but declined the insertion of an IUD for EC and/or had contraindications to IUD insertion
- Willing to abstain from further acts of UPI during participation in the study and until pregnancy status was ascertained

The exclusion criteria included:

- One or more acts of UPI more than 120 hours before requesting EC in the current cycle
- Currently pregnant as confirmed by positive HSUP test performed at Screening (Treatment Visit)
- Currently breast-feeding
- Current use of hormonal contraception
- Use of hormonal EC since last menstrual period
- Current use of IUD
- Tubal ligation

- Partner with a vasectomy
- Unsure about the date of the last menstrual period
- Severe asthma insufficiently controlled by oral glucocorticoid
- Currently enrolled in any other trial of an investigational medicine
- Hypersensitivity to the active substance levonorgestrel or any of the excipients of the drug products used in the study

6.1.1.3. Study treatments

1. Ulipristal acetate 30 mg tablet
2. Levonorgestrel 1.5 mg tablet

Treatments were administered as a single dose within 120 hours of unprotected intercourse.

6.1.1.4. Efficacy variables and outcomes

The primary efficacy outcome measure was the pregnancy rate when ulipristal 30 mg is administered within 72 hours of UPI is statistically significantly lower than the estimated expected pregnancy rate in the absence of EC. The secondary efficacy outcome measures were:

- The pregnancy rate when ulipristal 30 mg is administered within 120 hours of UPI
- The pregnancy rate when ulipristal 30 mg is administered within 72 hours of UPI in comparison with the 4% rate considered as the clinical irrelevance threshold
- The pregnancy rate when ulipristal 30 mg is administered within 120 hours of UPI in comparison with the 4% rate considered as the clinical irrelevance threshold
- Test of non-inferiority for ulipristal 30 mg in comparison with levonorgestrel 1.5 mg as emergency contraception within 72 hours of UPI
- Test of non-inferiority for ulipristal 30 mg in comparison with levonorgestrel 1.5 mg as emergency contraception within 120 hours of UPI
- Trend in pregnancy rates over time since intercourse
- Contraceptive effectiveness (prevented fraction) between treatment groups
- Effect of ulipristal 30 mg on the menstrual cycle compared to levonorgestrel 1.5 mg

The safety outcome measure was AEs.

The number of expected pregnancies was determined based on conception probabilities by cycle day of intercourse (Trussell et al. 1998). The expected pregnancy rate was determined to be 8%, and a halving of this rate (a reduction of 4%) was considered to be clinically meaningful.

6.1.1.5. Randomisation and blinding methods

Subjects were block randomised, stratified by study centre.

6.1.1.6. Analysis populations

The efficacy analysis was performed for the modified intention to treat (mITT) population. The mITT population included all subjects:

- Randomized and received study drug
- Had at least one UPI in the current cycle before enrolment
- Participated for the first time in the current study

- Known pregnancy status using high sensitivity urinary pregnancy (HSUP) test after EC intake (not lost-to-follow-up at follow-up Visits 1 & 2)
- 35 years of age or younger
- If pregnant, pregnancy not identified as started before EC intake (as measured by pre-treatment serum β -hCG level and gestational age confirmed by transvaginal ultrasound) or as "not compatible" with an EC failure, based on independent evaluation as assessed by DSMB

The primary efficacy analysis was to be conducted on the first 1200 subjects that completed the study.

6.1.1.1.7. *Sample size*

The sample size was estimated in order to reach at least 85% power for both primary and main secondary efficacy analyses: inferiority to clinical irrelevance threshold and the non-inferiority analysis of ulipristal 30 mg versus levonorgestrel 1.5 mg as EC within 72 hours of UPI.

Based on previous similar clinical trials, pregnancy rates in the ulipristal and levonorgestrel group were expected to be 1% and 1.7% respectively. In order to demonstrate the non-inferiority of CDB-2914 to levonorgestrel for subjects within 72 hours of UPI, 827 subjects per treatment group were needed. For this comparison, the non-inferiority margin was set to 1.6 in odds ratio with a type I error rate of 5% (two-sided) and 85% power. A non-inferiority margin of 1.6 in odds ratio was stated to be equivalent to a non-inferiority margin of 1% in percent point with an assumed pregnancy rate with levonorgestrel of 1.7%. In order to compensate for an anticipated lost to follow-up rate of 10%, 910 subjects per group were included in the 0-72 hour time interval.

6.1.1.1.8. *Statistical methods*

The 95% CI of the pregnancy rate was constructed using Agresti and Coull method. Logistic regression was used to investigate the trend of pregnancy rate and to estimate the odds ratios for some cofactors. The chi-square test was used for sensitivity analysis to confirm results obtained from the primary efficacy analysis.

The non-inferiority of ulipristal 30 mg versus levonorgestrel 1.5 mg as EC was concluded if the upper bound of the 95% CI of the odds ratio of pregnancy in the ulipristal group and the levonorgestrel group is lower than the non-inferiority margin of 1.6. Superiority was established if the upper bound of the 95% CI of the odds ratio is below 1.0.

6.1.1.1.9. *Participant flow*

There were 2321 subjects screened and 2221 were randomised to treatment: 1104 to ulipristal and 1117 to levonorgestrel. All scheduled study visits were completed by 1013 (91.8%) subjects in the ulipristal group and 1046 (93.6%) in the levonorgestrel (Figure 7.1.1.1).

6.1.1.1.10. *Major protocol violations/deviations*

One subject in the ulipristal group and two in the levonorgestrel were excluded from the mITT population because of pregnancy not compatible per DSMB.

6.1.1.1.11. *Baseline data*

The age range of the study subjects was 16 to 55 years. The treatment groups were similar in demographic characteristics. The treatment groups were similar in gynaecological history and time from UPI to treatment.

6.1.1.1.12. *Results for the primary efficacy outcome*

The primary efficacy analysis was based on the first 1200 subjects in the mITT population. The observed pregnancy rate (95% CI) within 72 hours of UPI for ulipristal was 1.51% (0.62% to

3.32%), whereas the expected pregnancy rate was 5.63%. The observed pregnancy rate (95% CI) for levonorgestrel was 2.81% (1.54%, 4.97%), whereas the expected pregnancy rate was 5.88%.

6.1.1.13. *Results for other efficacy outcomes*

- Up to 72 hours post UPI the pregnancy rate (95% CI) in the mITT population for ulipristal was 1.78 (1.04 to 2.98) %, which was significantly lower than the expected pregnancy rate of 5.54%. The pregnancy rate (95% CI) in the mITT population for levonorgestrel was 2.59 (1.68 to 3.94) %, which was significantly lower than the expected pregnancy rate of 5.43%.
- Up to 120 hours post UPI the pregnancy rate (95% CI) in the mITT population for ulipristal was 1.60 (0.93 to 2.67) %, which was significantly lower than the expected pregnancy rate of 5.72%. The pregnancy rate (95% CI) in the mITT population for levonorgestrel was 2.62 (1.75 to 3.89) %, which was significantly lower than the expected pregnancy rate of 5.52%.
- The upper bounds of the 95% CI for pregnancy rates at 72 hours and 120 hours, for ulipristal in the mITT population, were both below the clinical relevance threshold of 4%.
- Ulipristal was non-inferior to levonorgestrel at 72 hours and 120 hours post UPI. The OR (95% CI) for pregnancy for ulipristal in comparison with levonorgestrel was:
 - For the interim mITT population at 72 hours: 0.53 (0.20 to 1.44)
 - For the mITT population at 72 hours: 0.68 (0.35 to 1.31)
 - For the interim mITT population at 120 hours: 0.59 (0.31 to 1.14)
 - For the mITT population at 120 hours: 0.69 (0.36 to 1.32)

In each case the upper 95% CI was less than the predefined level of non-inferiority of 1.6.

- The pregnancy rates over time for ulipristal were 1.60% for the 0 to 24 hour time interval, 2.12% for the 24 to 48 hour interval and 1.48% for the >48 to 72 hour interval. No pregnancies were observed at the >72 to 96 and >96 to 120 hour intervals.
- At 72 hours after UPI the prevention fraction (95% CI) was 68.1 (45.8 to 81.2) % for ulipristal and 52.2 (25.1 to 69.5) % for levonorgestrel
- At 120 hours after UPI the prevention fraction (95% CI) was 72.2 (52.8 to 83.7) % for ulipristal and 52.8 (27.8 to 69.2) % for levonorgestrel
- In the time interval >72 to 120 hours after UPI the prevention rate was significantly greater for ulipristal than for levonorgestrel: 0.07736 for ulipristal compared with 0.4514 for levonorgestrel, $p = 0.0374$

An exploratory analysis was performed to evaluate the effects of investigator, age, time from intercourse to treatment, glucocorticoid use and further UPI post treatment intake. Age had an effect on pregnancy rate as did further UPI post treatment. However, these effects would not influence the choice of treatment.

6.1.2. *Other efficacy studies*

6.1.2.1. *Study HRA2914-509*

Study HRA2914-509 was a multicentre, open-label, single arm, study to assess the efficacy, safety and tolerance of a single dose of EC. The study was conducted at 40 sites by 16 investigators in the US from November 2006 to March 2008.

The inclusion criteria included:

- Women, ≥ 18 years of age

- Regular menstrual cycle (between 24 and 35 days) and intra-individual variations less than or equal to 5 days
- Emergency contraception requested between 48 hours and 120 hours after UPI. UPI was defined by lack of contraceptive use, condom breakage (including condoms lubricated with spermicide) or other barrier contraceptive method failure
- No current use of hormonal contraception and at least one complete menstrual cycle (two menses) since hormonal contraception was stopped
- If there was a recent history of Depo Provera use, the most recent injection was to be at least 9 months before study entry and followed by at least one complete menstrual cycle (two menses)
- Willing not to use hormonal methods of contraception until study completion
- At least one complete menstrual cycle (two menses) post delivery, miscarriage or abortion
- Willing to abstain from further acts of UPI during participation in the study and until pregnancy status was ascertained

The exclusion criteria included:

- One or more acts of one UPI more than 120 hours before requesting emergency contraception in the current cycle
- All acts of UPI (in the current cycle) within 48 hours of presentation
- Currently pregnant as confirmed by positive HSUP test performed at Screening/Treatment Visit
- Currently breast-feeding
- Current use of hormonal contraception
- Use of hormonal emergency contraception since last menstrual period
- Current use of IUD
- Tubal ligation
- Partner with a vasectomy
- Unsure about the date of the last menstrual period
- Severe asthma insufficiently controlled by oral glucocorticoid

The study treatment was ulipristal acetate 30 mg micronised tablet administered as a single dose between 48 and 120 hours of UPI.

The primary efficacy outcome measure was the pregnancy rate observed after taking ulipristal 30 mg between 48 hours and 120 hours of UPI compared with the estimated expected pregnancy rate in the absence of EC. The secondary efficacy outcome measures were:

- The pregnancy rate when ulipristal 30 mg is administered between 48 and 120 hours of UPI in comparison with the 4% rate considered as the clinical irrelevance threshold
- Trend in pregnancy rates over time since intercourse
- Contraceptive effectiveness (prevented fraction) between treatment groups
- Effect of ulipristal 30 mg on the menstrual cycle

Safety was measured using AEs.

There were 1623 subjects consented, 1533 were treated of whom 1507 were eligible for the study. Of the treated subjects, 1362 (88.8%) completed all scheduled visits. There were 1533 subjects in the ITT dataset and 1343 in the ITT completers dataset. The age range was 18 to 50 years, 921 (60.3%) subjects were White and 328 (21.5%) were Black or African American. There were 615 (40.1%) subjects treated in the >72 to 120 hours post UPI time window.

The observed pregnancy rate (95% CI) was 2.10 (1.41 to 3.10) % compared to the expected pregnancy rate of 5.53%. The upper 95% CI for pregnancy rate was below the clinically relevant threshold of 4%. The estimated pregnancy rate were 1.61% at 48 to 60 hours, 2.85% at 61 to 72 hours, 2.90% at 73 to 84 hours, 1.38% at 85 to 96 hours, 1.21% at 97 to 108 hours and 1.31% at 109 to 120 hours. The number of observed pregnancies was 26. The number of expected pregnancies was 69, and the prevented fraction (95% CI) was 62.32 (41.89 to 75.56) %. Further UPI after treatment increased the risk of pregnancy (OR 5.691), but there was no effect for age, investigator, time from UPI to treatment or glucocorticoid use.

6.1.2.2. Study HRA2914-515

Study HRA2914-515 was a multicentre, open label, single arm, observational study to assess the safety and tolerability of ulipristal in routine conditions of use for EC in post menarcheal adolescents and adult women in particular menorrhagia, metrorrhagia, dysmenorrhoea and effect on menstrual cycles. The study was conducted at 36 sites in Sweden, UK, France, US and Germany from December 2010 to January 2013. The study included subjects receiving ulipristal 30 mg as EC; post menarcheal adolescents or adult women in Sweden, France, the US and Germany and aged from 13 years in the United Kingdom. The study treatment was Ulipristal acetate, 30 mg tablet, by oral administration. There were 1310 subjects approached and 579 included in the study. The age range was 13 to 46 years: 279 were aged <18 years and 76 were <16 years. A total of 423 (73.1%) subjects completed the study: 140 subjects were lost to follow-up. There were seven (1.5%) pregnancies. There were 50 (10.8%) subjects that had further UPI during the treatment cycle.

6.1.3. Analyses performed across trials (pooled analyses and meta-analyses)

Study HRA2914 was a pooled analysis of data from Study HRA2914-004 and Study HRA2914-507. These studies used different doses and formulations of ulipristal. Hence the analysis does not contribute additional useful efficacy data, in addition to that already contributed by Study HRA2914-004, relating to the product proposed for marketing. The study did find that the risk of pregnancy is increased by increasing BMI, increased conception probability and by further UPI. In obese grade II individuals the risk of pregnancy was 3.64% and in obese grade III individuals the risk was 5.56%.

Study HRA2914-5001 was a further analysis of the effect of body weight on efficacy. The data were pooled from Study HRA2914-508, Study HRA2914-507 and Study HRA2914-513 and Study HRA2914-509. The analysis concluded that in women 72 kg or more, ulipristal appeared to be more efficacious than levonorgestrel² and that there was no identifiable weight threshold for the efficacy of ulipristal.

6.2. Evaluator's conclusions on efficacy for emergency contraception

In the pivotal study (Study HRA2914-513), ulipristal 30 mg as a single dose was demonstrated to have efficacy in comparison with expected pregnancy rates, and non inferiority in comparison with levonorgestrel when administered up to 120 h post UPI. There were the following efficacy findings:

- The observed pregnancy rate (95% CI) within 72 h of UPI for ulipristal was 1.51% (0.62% to 3.32%), whereas the expected pregnancy rate was 5.63%

² The sponsor points out these results were not statistically significant.

- Up to 120 h post UPI the pregnancy rate (95% CI) was 1.60 (0.93 to 2.67) %, which was significantly lower than the expected pregnancy rate of 5.72%.
- The upper bounds of the 95% CI for pregnancy rates at 72 h and 120 h, for ulipristal in the mITT population, were both below the clinical relevance threshold of 4%.
- Ulipristal was non inferior to levonorgestrel at 72 h and 120 h post UPI. The observed rate (OR) (95% CI) for pregnancy for ulipristal in comparison with levonorgestrel was:
 - For the interim mITT population at 72 h: 0.53 (0.20 to 1.44)
 - For the mITT population at 72 h: 0.68 (0.35 to 1.31)
 - For the interim mITT population at 120 h: 0.59 (0.31 to 1.14)
 - For the mITT population at 120 h: 0.69 (0.36 to 1.32)

In each case, the upper 95% CI was less than the predefined level of non inferiority of 1.6.

- The pregnancy rates over time for ulipristal were 1.60% for the 0 to 24 h time interval, 2.12% for the 24 to 48 h interval and 1.48% for the >48 to 72 h interval. No pregnancies were observed at the >72 to 96 and >96 to 120 h intervals.
- At 72 h after UPI, the prevention fraction (95% CI) was 68.1 (45.8 to 81.2) % for ulipristal and 52.2 (25.1 to 69.5) % for levonorgestrel.
- At 120 h after UPI, the prevention fraction (95% CI) was 72.2 (52.8 to 83.7) % for ulipristal and 52.8 (27.8 to 69.2) % for levonorgestrel.
- In the time interval >72 to 120 h after UPI, the prevention rate was significantly greater for ulipristal than for levonorgestrel: 0.07736 for ulipristal compared with 0.4514 for levonorgestrel, $p = 0.0374$.

The supportive efficacy studies demonstrated similar pregnancy rates and prevention fraction to the pivotal study. In Study HRA2914-509, the observed pregnancy rate (95% CI) was 2.10 (1.41 to 3.10) % compared to the expected pregnancy rate of 5.53%. The upper 95% CI for pregnancy rate was below the clinically relevant threshold of 4%. The estimated pregnancy rates were 1.61% at 48 to 60 h, 2.85% at 61 to 72 h, 2.90% at 73 to 84 h, 1.38% at 85 to 96 h, 1.21% at 97 to 108 h, and 1.31% at 109 to 120 h. The prevented fraction (95% CI) was 62.32 (41.89 to 75.56) %. In Study HRA2914-515, the pregnancy rate was 1.5%.

Efficacy was decreased by further UPI after treatment (OR 5.691). Although increasing BMI (body mass index) decreased efficacy, there was no identifiable weight threshold.

The clinical studies were conducted in a population similar to that intended in the proposed indication. The criterion for non inferiority was appropriate. The dose and indication for the active comparator (levonorgestrel) was appropriate.

7. Clinical safety

7.1. Studies providing safety data

The following studies provided evaluable safety data.

7.2. Studies providing evaluable safety data

The following studies provided evaluable safety data:

7.2.1. Pivotal efficacy studies

In the pivotal efficacy study, the following safety data were collected:

- General adverse events (AEs)
- Menstrual symptoms
- Routine laboratory tests were not performed

7.2.2. Pivotal studies that assessed safety as a primary outcome

Study HRA2914-515 was a multicentre, open label, single arm, observational study to assess the safety and tolerability of ulipristal in routine conditions of use for EC in post menarcheal adolescents and adult women in particular menorrhagia, metrorrhagia, dysmenorrhoea and effect on menstrual cycles.

7.2.3. Dose-response and non-pivotal efficacy studies

The dose-response and non-pivotal efficacy studies provided safety data, as follows:

- General adverse events (AEs)
- Nausea / vomiting
- Menstrual symptoms
- Routine laboratory tests were not performed

7.2.4. Clinical pharmacology studies

- General adverse events (AEs)
- Routine laboratory tests

7.3. Pivotal studies that assessed safety as a primary outcome

See above.

7.4. Patient exposure

In Study HRA2914-507, there were: 832 subjects treated with 50 mg ulipristal as a single dose.

In Study HRA2914-508, there were 399 subjects treated with a single dose of 10 mg micronised ulipristal and 413 treated with a single dose of 50 mg unmicronised ulipristal.

In Study HRA2914-513, a total of 1104 subjects were exposed to a single dose of 30 mg ulipristal.

In Study HRA2914-509, there were 1533 subjects exposed to ulipristal 30 mg on at least one occasion, with 66 subjects treated on two occasions and nine on three.

In Study HRA2914-515, there were 579 subjects treated with ulipristal 30 mg. There were 279 subjects aged <18 years and 76 aged <16 years.

7.5. Adverse events

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

7.5.1.1. Pivotal studies

In Study HRA2914-513, 1506 TEAEs were reported in 597 (54.1%) subjects treated with ulipristal and 1629 in 626 (56.0%) subjects treated with levonorgestrel. The pattern of AEs was

similar for the two treatment groups and the most commonly reported TEAEs were headache, dysmenorrhoea and nausea (Table 3).

Table 3: AEs (Preferred Term) Reported in $\geq 1\%$ of the Subjects (Study HRA2914-513).

PREFERRED TERM	CDB-2914 N=1104	LEVONORGESTREL N=1117
HEADACHE	213 (19.3%)	211 (18.9%)
DYSMENORRHOEA	142 (12.9%)	160 (14.3%)
NAUSEA	141 (12.8%)	126 (11.3%)
ABDOMINAL PAIN	56 (5.1%)	75 (6.7%)
DIZZINESS	57 (5.2%)	55 (4.9%)
FATIGUE	61 (5.5%)	44 (3.9%)
ABDOMINAL PAIN UPPER	37 (3.4%)	46 (4.1%)
NASOPHARYNGITIS	31 (2.8%)	32 (2.9%)
BACK PAIN	35 (3.2%)	27 (2.4%)
ABDOMINAL PAIN LOWER	21 (1.9%)	35 (3.1%)
BREAST TENDERNESS	20 (1.8%)	19 (1.7%)
VAGINAL DISCHARGE	17 (1.5%)	17 (1.5%)
DIARRHOEA	16 (1.4%)	17 (1.5%)
ABDOMINAL DISTENSION	17 (1.5%)	14 (1.3%)
VOMITING	17 (1.5%)	12 (1.1%)
MIGRAINE	13 (1.2%)	15 (1.3%)
PHARYNGOLARYNGEAL PAIN	9 (0.8%)	16 (1.4%)
SEASONAL ALLERGY	14 (1.3%)	9 (0.8%)
SOMNOLENCE	10 (0.9%)	12 (1.1%)

7.5.1.2. Other studies

In Study HRA2914-510, with continuous treatment over 12 weeks, TEAEs were reported in ten (83.3%) in the 2.5 mg group, eleven (91.7%) in the 5 mg, eleven (100%) in the 10 mg and nine (81.8%) in the placebo. Ovarian cyst >20 mm was reported in two (16.6%) in the 2.5 mg group, six (50.0%) in the 5 mg, nine (81.8%) in the 10 mg and one (9.1%) in the placebo. Headache was more common in the ulipristal groups: six (50.0%) in the 2.5 mg group, five (41.7%) in the 5 mg, four (36.4%) in the 10 mg and two (18.2%) in the placebo.

In Study HRA2914-554, 39 TEAEs were reported in 11 (91.7%) subjects in the weekly group and 29 in 11 (100%) in the every 5 days group. Headache was reported in 10 (43.5%) subjects, and anaemia in 4 (17.4%).

In Study HRA2914-507, TEAEs were reported in 639 (77%) subjects in the ulipristal group and 636 (76%) in the levonorgestrel. The pattern of TEAEs was similar for the two treatment groups. The commonest TEAEs in the ulipristal group were: fatigue, headache, nausea, dizziness, uterine pain, breast tenderness and diarrhoea.

In Study HRA2914-508, TEAEs were reported in 315 (78.9%) subjects in the 10 mg micronised group and 314 (76.0%) in the unmicronised 50 mg group. The commonest TEAEs were: headache, nausea, uterine pain, fatigue, dizziness, breast tenderness and menstrual irregularity.

In Study HRA2914-509, there were 2232 TEAEs reported in 876 (61.4%) subjects. The commonest TEAEs were headache (17.5% subjects), nausea (12.2%), and abdominal pain (11.7%).

In Study HRA2914-515, there were 350 TEAEs in 148 (31.4%) subjects: 47 in 19 (29.7%) in the < 16 years group and 171 in 68 (28.5%) in the <18 years group. The most common TEAE was headache, occurring in 10.8% subjects. Upper abdominal pain was more common in the <16 years age group: 7.8% subjects compared with 2.5%.

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

7.5.2.1. Pivotal studies

In Study HRA2914-513, TEAEs certainly, probably or possibly related to treatment were reported in 286 (33.4%) subjects in the ulipristal group and 307 (35.4%) in the levonorgestrel.

The pattern of these TEAEs was similar for the two groups, and no single event occurred in $\geq 10\%$ in either study group.

7.5.2.2. *Other studies*

In Study HRA2914-509, the commonest TEAEs attributed to study treatment were headache (10.6% subjects) and nausea (10.5%).

In Study HRA2914-515, two TEAEs certainly related to study medication were reported in one (0.2%) subject, there were 35 in 23 (4.9%) probably related to study medication and 70 in 39 (8.3%) possibly related to study medication.

7.5.3. *Deaths and other serious adverse events*

7.5.3.1. *Pivotal studies*

In Study HRA2914-513, there were no deaths reported during the study. There were three SAEs in the ulipristal group: urinary tract infection, right contact lens related corneal ulcer and dizziness; and four in the levonorgestrel: vomiting blood stained fluid, molar pregnancy, ruptured ovarian cyst, and kidney stones.

7.5.3.2. *Other studies*

In Study HRA2914-510, with continuous treatment over 12 weeks, there were no deaths. There were two SAEs: abdominal pain/fever and Grave's disease.

In Study HRA2914-554, there were no deaths, and no SAEs.

In Study HRA2914-507, there were no deaths. There were two SAEs, both in the ulipristal group: kidney infection and pelvic inflammatory disease.

In Study HRA2914-508, there were no deaths or SAEs.

In Study HRA2914-509, there were no deaths. There was one SAE reported: seizures.

In Study HRA2914-515, there were no deaths reported. There was one SAE: viral infection.

7.5.4. *Discontinuation due to adverse events*

7.5.4.1. *Pivotal studies*

In Study HRA2914-513, two subjects in the ulipristal group discontinued because of AEs: vomiting and ruptured ovarian cyst.

7.5.4.2. *Other studies*

In Study HRA2914-510, with continuous treatment over 12 weeks, there was one DAE: abdominal pain/fever.

In Study HRA2914-554, Study HRA2914-507, Study HRA2914-508, Study HRA2914-509, and Study HRA2914-515, there were no DAEs reported.

7.6. *Laboratory tests*

In Study HRA2914-507 and Study HRA2914-513, laboratory tests were not performed as a safety outcome measure.

7.6.1. *Liver function*

No clinically significant abnormalities in liver function were reported.

7.6.2. *Kidney function*

No clinically significant abnormalities in renal function were reported.

7.6.3. Other clinical chemistry

No clinically significant abnormalities in other clinical chemistry were reported.

7.6.4. Haematology

In Study HRA2914-554, protein C, protein S, APC resistance test, and SHBG remained within normal limits in all subjects. However, four subjects developed anaemia.

7.6.5. Nausea and vomiting

In Study HRA2914-507, at a 50 mg dose level, there was a greater proportion of subjects with nausea in the ulipristal group: 237 (30%) subjects compared with 186 (24%) in the levonorgestrel ($p = 0.008$). The nausea was more likely on Days 1 and 2 post-dose. However, vomiting was reported in 19 (2%) subjects in the ulipristal group and 14 (2%) in the levonorgestrel.

In Study HRA2914-508, nausea was reported in 122 (30.6%) subjects in the 10 mg micronised group and 90 (21.8%) in the 50 mg unmicroised. Nausea was more common on Day 1 post dose. There were few reports of vomiting: on Day 1 seven (2%) subjects in the 10 mg micronised group and six (1%) in the 50 mg unmicroised.

7.6.6. Effects on the menstrual cycle

7.6.6.1. Pivotal studies

In Study HRA2914-513, the mean (SE) change in menstrual cycle length was 2.3 (0.3) days in the ulipristal group and -1.5 (0.3) days in the levonorgestrel. There were 40 (4.7%) subjects in the ulipristal group and 19 (2.2%) in the levonorgestrel with amenorrhoea follow-up. Menses had not returned by 60 days for three subjects in the ulipristal group, and none in the levonorgestrel. Vaginal bleeding was similar for the two treatment groups.

7.6.6.2. Other studies

In Study HRA2914-507, at a 50 mg dose level, ulipristal increased cycle length by a mean (SD) of 2.8 (9.15) days, whereas levonorgestrel decreased cycle length by 2.1 (7.82) days.

Mean (SD) change in cycle length was 1.4 (7.56) days for the 10 mg micronised group and 2.0 (8.31) days for the 50 mg unmicroised. There was no difference between the treatment groups in menstrual symptoms.

In Study HRA2914-509, the mean (SE) change in cycle length was 2.9 (0.3) days. In eight subjects menses had not returned within 60 days of follow-up visit 2. Intermenstrual bleeding was reported in 134 (8.7%) subjects, and for 123 of these subjects the bleeding was described as spotting.

In Study HRA2914-515, dysmenorrhoea was reported in nine (1.9%) subjects, menorrhagia in 140 (19.7%) and metrorrhagia in 99 (21.0%). The treatment cycle was increased by >7 days in 174 (45.2%) subjects. The mean (SD) increase in treatment cycle was 9.9 (14.6) days. The mean (SD) increase in post-treatment cycle was 5.9 (6.7) days.

Study HRA2914-558 was a pooled analysis of data from Study 2914-509 and Study 2914-513. There were two analyses presented. The larger dataset contained 1533 subjects, of whom 134 (8.7%) had intermenstrual bleeding: 127 (94.8%) spotting, five (3.7%) regular and two (1.5%) heavy.

7.7. Post-marketing experience

7.7.1. Post-marketing data

There were seven PSURs covering the time period 15 May 2009 to 14 May 2013. There was no regulatory action for safety reasons over this time period. Over this time period the Sponsor

estimates 1,434,781 packs have been sold worldwide. The case reports were predominantly of unintended pregnancy. Other than pregnancy or drug exposure during pregnancy, the serious medically confirmed unlisted reactions were one case of syncope, one case of viral infection, one case of grand-mal seizure, and one case of haemorrhage (unknown site). Since IBD the Sponsor has received 282 reports of pregnancy. There were 149 reports of unintended pregnancy. The results for these 149 cases were: healthy newborn for four, spontaneous abortion for eight, elective abortion for 39, ectopic pregnancy for two, six were ongoing and 90 were lost to follow-up.

Study HRA2914-648 was a retrospective, post-marketing analysis of pregnancies due to inadvertent exposure or treatment failure. The study used data from Planned Parenthood Columbia Willamette, a group of clinics in the US. There were 55 pregnancies identified from the clinic database. The age range was 18 to 42 years and mean (SD) BMI was 25.4 (4.5). The outcome of the pregnancies was: induced abortion for 33, spontaneous abortion 2, ectopic pregnancy 1, and continuation of pregnancy in 9. There were 10 subjects lost to follow-up.

7.7.2. Risk Management Plan

In the Risk Management Plan the Sponsor has stated there are no Important Identified Risks.

The Important Potential Risks are:

- Effects on pregnancy maintenance/off label use
- Risk of incomplete abortion and heavy bleeding
- Effects on foetus and newborns
- Risk of ectopic pregnancy
- Concomitant use of CYP3A4 inducers
- Liver effects
- Delayed menstrual period >60 days / amenorrhea
- Ovarian cysts

The Missing Information is:

- Effect of concomitant use of progestin-only contraception
- Effect in patients with severe asthma treated by oral glucocorticoid
- Effects in women with impaired liver function

The sponsor intends to address these issues with:

- Routine pharmacovigilance
- Specific report forms for pregnancy; incomplete abortion/heavy bleeding; and hepatic adverse events
- Web based pregnancy registry with online questionnaire and access to HCPs and women

7.8. Safety issues with the potential for major regulatory impact

7.8.1. Use in younger age groups

Study HRA-2914-555 was a pooled analysis that investigated the safety profile in subjects <18 years of age. In 44 subjects aged <18 years, the most frequent AEs were nausea in four (9.09%) subjects and headache in three (6.82%).

7.8.2. Effects on the foetus

There were insufficient completed pregnancies reported in the data to be able to make any conclusions with regard to safety for the foetus and newborn.

7.9. Evaluator's conclusions on safety

Ulipristal appears to have a favourable safety profile. The most commonly reported AEs were headache, nausea and abdominal pain. There is some prolongation of the menstrual cycle consistent with the mechanism of action and pharmacodynamic data. There were few serious adverse events (SAEs) or AEs leading to discontinuation (DAEs).

The 'Adverse Effects' section of the PI document is supported by the data presented in the submission.

8. First round benefit-risk assessment

8.1. First round assessment of benefits

In the pivotal study (Study HRA2914-513), ulipristal 30 mg as a single dose was demonstrated to have efficacy in comparison with expected pregnancy rates, and non inferiority in comparison with levonorgestrel when administered up to 120 h post UPI. There were the following efficacy findings:

- The observed pregnancy rate (95% CI) within 72 h of UPI for ulipristal was 1.51% (0.62% to 3.32%), whereas the expected pregnancy rate was 5.63%.
- Up to 120 h post UPI, the pregnancy rate (95% CI) was 1.60 (0.93 to 2.67) %, which was significantly lower than the expected pregnancy rate of 5.72%.
- The upper bounds of the 95% CI for pregnancy rates at 72 h and 120 h, for ulipristal in the mITT population, were both below the clinical relevance threshold of 4%.
- Ulipristal was non-inferior to levonorgestrel at 72 h and 120 h post UPI. The OR (95% CI) for pregnancy for ulipristal in comparison with levonorgestrel was:
 - For the interim mITT population at 72 h: 0.53 (0.20 to 1.44)
 - For the mITT population at 72 h: 0.68 (0.35 to 1.31)
 - For the interim mITT population at 120 h: 0.59 (0.31 to 1.14)
 - For the mITT population at 120 h: 0.69 (0.36 to 1.32)

In each case, the upper 95% CI was less than the predefined level of non-inferiority of 1.6.

- The pregnancy rates over time for ulipristal were 1.60% for the 0 to 24 h time interval, 2.12% for the 24 to 48 h interval and 1.48% for the >48 to 72 h interval. No pregnancies were observed at the >72 to 96 and >96 to 120 h intervals.
- At 72 h after UPI, the prevention fraction (95% CI) was 68.1 (45.8 to 81.2) % for ulipristal and 52.2 (25.1 to 69.5) % for levonorgestrel.
- At 120 h after UPI, the prevention fraction (95% CI) was 72.2 (52.8 to 83.7) % for ulipristal and 52.8 (27.8 to 69.2) % for levonorgestrel.
- In the time interval >72 to 120 h after UPI, the prevention rate was significantly greater for ulipristal than for levonorgestrel: 0.07736 for ulipristal compared with 0.4514 for levonorgestrel, $p = 0.0374$.

The supportive efficacy studies demonstrated similar pregnancy rates and prevention fraction to the pivotal study. In Study HRA2914-509, the observed pregnancy rate (95% CI) was 2.10 (1.41 to 3.10) % compared to the expected pregnancy rate of 5.53%. The upper 95% CI for pregnancy rate was below the clinically relevant threshold of 4%. The estimated pregnancy rates were 1.61% at 48 to 60 h, 2.85% at 61 to 72 h, 2.90% at 73 to 84 h, 1.38% at 85 to 96 h, 1.21% at 97 to 108 h, and 1.31% at 109 to 120 h. The prevented fraction (95% CI) was 62.32 (41.89 to 75.56) %. In Study HRA2914-515, the pregnancy rate was 1.5%.

Efficacy was decreased by further UPI after treatment (OR 5.691). Although increasing BMI decreased efficacy, there was no identifiable weight threshold.

The clinical studies were conducted in a population similar to that intended in the proposed indication. The criterion for non inferiority was appropriate. The dose and indication for the active comparator (levonorgestrel) was appropriate.

8.2. First round assessment of risks

Ulipristal appears to have a favourable safety profile. The most commonly reported AEs were headache, nausea and abdominal pain. There is some prolongation of the menstrual cycle consistent with the mechanism of action and pharmacodynamic data. There were few SAEs or DAEs.

8.3. First round assessment of benefit-risk balance

The benefit-risk balance of EllaOne (ulipristal acetate) 30 mg tablets, given the proposed usage, is favourable.

9. First round recommendation regarding authorisation

The evaluator would have no objection to the approval of EllaOne (ulipristal acetate) 30 mg tablets for the indication of:

Emergency contraception within 120 hours (5 days) of unprotected sexual intercourse or contraceptive failure.

10. Clinical questions

No questions.

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