European Medicines Agency
Evaluation of Medicines for Human Use

Doc.Ref.: EMEA/261787/2009

CHMP ASSESSMENT REPORT

FOR

Ellaone

International Nonproprietary Name: ulipristal acetate

Procedure No. EMEA/H/C/001027

Assessment Report as adopted by the CHMP with
all information of a commercially confidential nature deleted.

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 75 23 70 51
E-mail: mail@emea.europa.eu http://www.emea.europa.eu

TABLE OF CONTENTS

1. BACKGROUND INFORMATION ON THE PROCEDURE

1.1. Submission of the dossier

The applicant Laboratoire HRA Pharma submitted on 30 May 2008 an application for Marketing Authorisation to the European Medicines Agency (EMEA) for Ellaone, through the centralised procedure under Article 3 (2) (a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMEA/CHMP on 28 March 2007.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application

The application submitted is a complete dossier composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

Scientific Advice:
The applicant did not seek scientific advice at the CHMP.

Licensing status:
The product was not licensed in any country at the time of submission of the application.

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:
Rapporteur: **Pieter de Graeff** Co-Rapporteur: **Tomas P Salmonson**

1.2. Steps taken for the assessment of the product

- The application was received by the EMEA on 30 May 2008.
- The procedure started on 26 June 2008.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 15 September 2008. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 19 September 2008. In accordance with Article 6(3) of Regulation (RC) No 726/2004, the Rapporteur and Co-Rapporteur declared that they had completed their assessment report in less than 80 days.
- During the meeting on 20-23 October 2008, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 24 October 2008.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 19 November 2008.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 22 December 2008.
- During the CHMP meeting on 19-22 January 2009, the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 13 February 2009.
- The Rapporteurs circulated the Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 02 March 2009.
- During the meeting on 16-19 March 2009 the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Ellaone on 19 March 2009. The applicant provided the letter of undertaking on the specific obligations and follow-up measures to be fulfilled post-authorisation on 17 March 2009.

2. SCIENTIFIC DISCUSSION

2.1. Introduction

Ellaone is a tablet containing 30 mg of micronized ulipristal acetate.

The proposed indication is: Emergency contraception within 120 hours (5 days) of unprotected sexual intercourse or contraceptive failure.

The proposed posology is one tablet to be taken orally as soon as possible, but no later than 120 hours (5 days) after unprotected intercourse or contraceptive failure.

Despite the availability of highly effective methods of contraception, many pregnancies are unplanned. Emergency contraception (EC), defined as treatments aimed at preventing pregnancy after unprotected sexual intercourse, is an important means of preventing unwanted pregnancy following unprotected intercourse (UPI). It is intended as a backup for occasional, emergency use only.

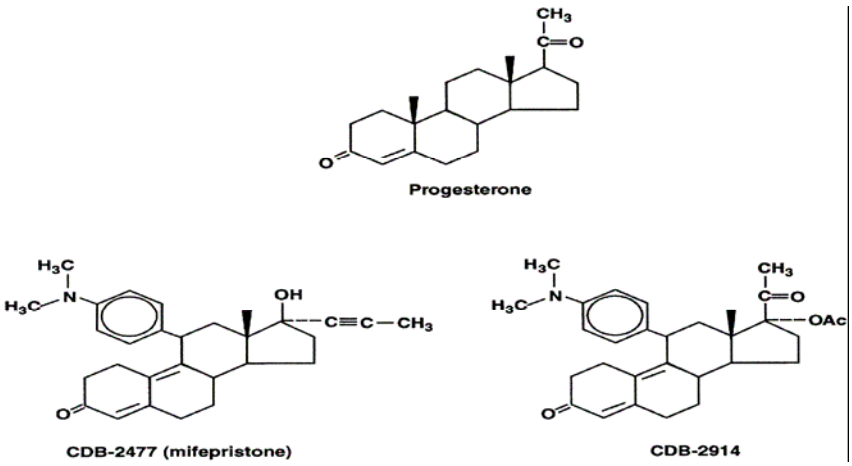
The history of emergency contraception dates back to the 1960s when hormonal regimens were first introduced.

- Following the introduction of high-dose oestrogens, the so-called Yuzpe regimen, involving the combined use of oestrogen (100 microgram ethinylestradiol) and progestogen (0.5 mg levonorgestrel or 1 mg dl-norgestrel) repeated once 12 hours apart with the first dose given within 72 hours of UPI, became popular in the late 70s and early 80s of last century[1]. The Yuzpe regimen was associated with a high incidence of nausea and vomiting due to the high oestrogen content.
- Since 1990s the potential of levonorgestrel, a synthetic progestagen, was recognised and was set to replace the previous Yuzpe regimen of combined high-dose oral contraceptives. Levonelle-2 and Norlevo were approved in a two dose regimen by a mutual recognition procedure (UK/H/363/01 and FR/H/146/01 respectively), i.e. two doses of 0.75 mg levonorgestrel, the first tablet to be taken within 72 hours of UPI and the second tablet 12 hours later. After studies showing the same efficacy of two doses of 0.75 mg levonorgestrel 12 hours apart compared with 1.5 mg levonorgestrel given at once, 1.5 mg tablets of levonorgestrel were also granted marketing authorisation by a mutual recognition procedure (Norlevo FR/H/146/02 and Levonelle 1500 µg UK/H/803/01).
- Recent interest in the development of alternative regimens has led to trials of the antigonadotropin danazol, and antiprogestogens including mifepristone[2], but not to marketing authorisation in the EU.
- Another option to prevent pregnancy after UPI is the postcoital insertion of a copper intra-uterine device (although not approved or labelled for such use) that can be used up to 5 days after the estimated time of ovulation, keeping it in the uterus as a long-term regular contraceptive method.

The chemical structures of progesterone, mifepristone and ulipristal (CDB-2914) are shown in the figure below.

[1] Yuzpe AA and Lancee WJ. Ethinylestradiol and dl-norgestrel as a postcoital contraceptive. Fertil Steril 1977;28:932-6.

[2] Webb AM, Russell J, and Elstein M. Comparison of Yuzpe regimen, danazol, and mifepristone (RU486) in oral postcoital contraception. BMJ 1992;305:927-31.



The National Institute of Child Health and Human Development (NICHD) initiated the clinical development phase of ulipristal acetate for use as an emergency contraception. The applicant, HRA Pharma, licensed the rights to the compound in 2000.
The application is therefore constituted of a mix of own studies from the applicant and studies submitted in the form of publications.

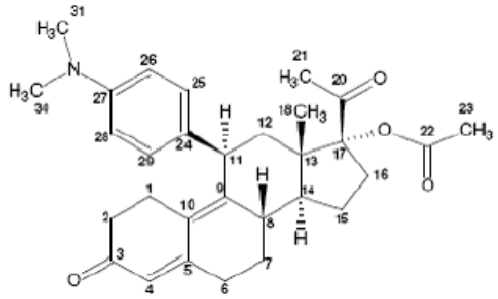
2.2. Quality aspects

Introduction

HRA Pharma has submitted an application for Ellaone 30mg tablet containing the new active substance ulipristal acetate. Other ingredients are lactose monohydrate, povidone K30, purified water, croscarmellose sodium, and magnesium stearate.
The tablets are packed in PVC/PE/PVDC blister sealed with aluminium foil.

Active Substance

Ulipristal acetate, or 17α-acetoxy-11α-(4-N,N-dimethylaminophenyl)-19-norpregna-4,9-diene-3,20-dione, is a white to yellow crystalline powder. It is freely soluble in methylene chloride, soluble in methanol, acetone and ethanol and insoluble in water.
The structure of the active substance ulipristal acetate is shown below.



Ulipristal acetate has 5 asymetric carbons but only the following absolute configuration of the chiral centers according is used : 8S, 11S, 13S, 14R, 17R.
Two polymorphs have been found

- Manufacture

Information about manufacturing process has been provided using Active Substance Master File (ASMF) procedure.

The four step synthesis has been well described.

Critical parameters and accompanying in-process controls have been defined. Adequate specification has been provided for all starting materials (reagents, solvents and auxiliary materials) and intermediates have been satisfactorily controlled. Impurities and degradation products have been investigated and fully justified by toxicological studies.

Batch analysis data produced with the proposed synthetic route provided show that the active substance can be manufactured reproducibly.

- Specification

The drug substance specification includes tests for description, identification (Infra-Red spectrum and HPLC), appearance of solution, melting point, loss on drying (Karl-Fischer), related substances (HPLC), assay (HPLC), residual solvents (GC), particle size distribution (laser-light scattering), optical rotation, heavy metals and polymorphic purity (Differential Scanning Calorimetry).

A satisfactory description for all analytical methods was provided. The methods are Ph Eur apart from related substances, assay, residual solvents, and particle size distribution, optical rotation and polymorphic purity. Full method validation data was provided for the non compendial (in-house) analytical methods

The particle size specification for the micronized drug substance drug substance is important to ensure a satisfactory dissolution and bioavailability behaviour.

Specification is appropriate and in accordance with ICH requirements. In particular, the impurity limits have been justified. The residual solvents limits are those of the ICH Q3C guideline or tighter.
Data on 7 non-consecutive batches of active substance used for clinical studies and for primary stability studies have been presented. All the results were found within the specification in particular for the impurities and the residual solvents.

The drug substance is packaged in double polyethylene film bags placed into high-density polyethylene drums. The drums used are opaque high density polyethylene containers; therefore, the product is stored in light-resistant containers. The container closure system has been adequately described and appropriate specification is present including IR identification,

- Stability

Stability studies for three validation-production batches were carried out according to ICH guidelines for real time (25°C/60% RH) and accelerated conditions (40°C/75% RH). The following parameters were studied: description, identification by IR, assay, loss on drying, related substances and optical rotation. The limits are the same as those proposed for release.
6 month data at 40°C/75% RH proves the stability of ulipristal acetate when stored under ICH accelerated conditions. The long-term stability study is due to last five years; all acceptance requirements are met for the 24 month results available as of today.
In summary, the stability data provided support the proposed re-test period.

Medicinal Product

- Pharmaceutical Development

Ulipristal acetate was evaluated with different formulations through phase I, II and III clinical trials. Based on comparative clinical bioavailability results and phase II studies, a 30mg immediate release tablet was developed. Taking into account the properties of the active substance and the requirements in terms of particle size distribution, the active substance is micronized and a wet granulation was developed.

The choice and the functions of the excipients that are in the final formulation have been described and justified. These are: lactose monohydrate (diluent), povidone K30 (binder), purified water (processing aid during wet granulation), croscarmellose sodium (disintegrating agent), and magnesium stearate (lubricant). All of them are controlled according to the current version of the Ph. Eur.
None of the materials used in the synthesis of ulipristal acetate active substance and excipients used in the tablets are of animal or human origin and therefore there is no risk of TSE contamination.

Ellaone tablets area packed in an immediate packaging obtained by sealing together:
- a transparent colourless 250 μm PVC/PE/PVDC Triplex foil ,
- a 20 μm aluminum foil. This foil is coated with heat sealing varnish on the inner face.
Packaging components comply with the current EU legislation.
No interaction between the tablets and the chosen immediate packaging material has been observed during stability studies.

- Manufacture of the Product

The tablets are manufactured according to a standard wet granulation process which involves (1) mixing of powders, (2) wetting, (3) granulation, (4) drying, (5) calibration, (6) mixing, (7) lubrication, (8) compression and (9) packaging. The manufacturing process is satisfactorily described and the in-process controls are adequate. A flow diagram and detailed description of the equipment have been provided.

At the time of submission validation protocol only was provided and supported by an evaluation of the manufacturing process performed on two pilot scale batches and one industrial batch. This is acceptable as according to CPMP/QWP/848/96, Note for Guidance on Process Validation, "it is recognised that, at the time of submission, process validation data may not always be available. Nevertheless it is essential that valid manufacturing processes are always utilised". The in-process control parameters were verified during the manufacture of pilot batches. Also the applicant committed to perform validation on the first three production scale batches.

- Product Specification

The product specification is standard for tablets and contains tests with suitable limits for appearance, identification (TLC and HPLC), mean mass, uniformity of dosage units (Ph. Eur.), impurities and degradation products (HPLC), dissolution (Ph. Eur.), disintegration (Ph. Eur.), microbial contamination (Ph. Eur.), and assay (HPLC).

Full details of all analytical methods are provided. All non pharmacopoeial methods have been satisfactory validated. Impurities have been appropriately controlled and their limits justified by toxicological studies. The proposed limits for individual degradation products is in line with the qualification and identification threshold in the ICH Q3B (R2) Impurities in New Drug Products and is well justified by real time data.

Batch analysis data have been provided for 2 development/clinical and 2 production batches; results comply with the proposed specification demonstrating the consistency of the process.

- Stability of the Product

The stability studies were carried out according to CPMP/ICH stability guidelines. 24 month at 30°C/60% RH stability data is available for 1 development and for 1 clinical batches, and 12 month at 30°C/60% RH stability data is available for a third one (clinical batch). The testing includes appearance, mean mass, impurities and degradation products, dissolution, disintegration, microbial contamination on packaged tablets and assay. All results comply with release specifications.

The proposed container-closure system is not light-proof and photostability stress study has not been performed on the packaged tablets. But taking into account the proposed indication and presentation (one tablet per blister), it is unlikely that the drug product is exposed to light; therefore inclusion of the recommendation "Keep in the outer carton in order to protect from light" in the storage conditions of the tablets is sufficient.

In general the results support the shelf life and storage conditions as defined in the SPC.

Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the drug substance and drug product have been presented in a satisfactory manner. The results of tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.

At the time of the CHMP opinion, there were a number of minor unresolved quality issues having no impact on the Benefit/Risk ratio of the product. The applicant gave a letter of Undertaking and committed to resolve these as Follow Up Measures after the opinion, within the agreed timeframe.

2.3. Non-clinical aspects

Pharmacology

Ulipristal acetate (17α-Acetoxy-11β-(4-N,N-dimethylaminophenyl)-19-norpregna-4,9-diene-3,20-dione, also known as CDB-2914, VA2914, HRP-2000 and RTI-3021-012) is a compound that is derived from 19-norprogesterone. It is a synthetic selective progesterone receptor modulator with antagonistic and partial agonistic effects at the progesterone receptor. It binds the human progesterone, but not the estrogen receptor[3]. Ulipristal acetate prevents progesterone from occupying its receptor, thus the gene transcription normally turned on by progesterone is blocked, and the proteins necessary to begin and maintain pregnancy are not synthesized.

- Primary pharmacodynamics

The primary pharmacodynamic data originates both from academic and contract laboratories, often in the form of publications in the scientific literature. The binding of ulipristal acetate to hormonal steroid receptors has been investigated in a number of studies in comparison with mifepristone, as shown in the table below. The relative binding affinity (RBA) is compared to a value of 100% for the reference agent (progesterone for the progesterone receptor, dexamethasone for the glucocorticoid receptor, estradiol for the estrogen receptor, dihydrotestosterone or methyltrienolone for the androgen receptor).

[3] Attardi BJ, Burgenson J, Hild SA, et al. In vitro antiprogestational/antiglucocorticoid activity and progestin and glucocorticoid receptor binding of the putative metabolites and synthetic derivatives of CDB-2914, CDB-4124, and mifepristone. J Steroid Biochem Mol Biol 2004;88:277-88.

Table: Summary of studies investigating the interaction of ulipristal acetate and mifepristone with steroid hormone receptors.

Parameter	Receptor affinity						Document
	PR[1]	hrPR-A[2]	hrPR-B[3]	GR[4]	ER[5]	AR[6]	
Ulipristal							
RBA (%)	87, 90, 116, 163, 183[a,*]	-	-	60, 176[d*]	<0.7[g]	15[k]	HRA2914-401
RBA (%)	607[c]	-	-	156[f]	<0.1[h]	21[k]	HRA2914-401
IC_{50} (nM)	4.2[b]	-	-	3.3[f]	6767[h]	17[k]	HRA2914-401
IC_{50} (nM)	13.5[b]	7.8	6.8	18.2[e]	-	65.5[m]	HRA2914-402
IC_{50} (nM)	13.6[b]	8.5	7.7	15.4[e]	-	-	HRA2914-449
Mifepristone							
RBA (%)	165, 178, 269[a*]	-	-	101, 262[d*]	<0.7[g]	14	HRA2914-401
IC_{50} (nM)	3.0[b]	-	-	1.6[f]	946[h]	10[k]	HRA2914-401
IC_{50} (nM)	11.5[b]	9.6	7.8	10.0[e]	-	13[k]	HRA2914-402
IC_{50} (nM)	11.5[b]	10.6	9.5	9.1[e]	-	-	HRA2914-449

[1] progesterone receptor - [a] rat uterus, [b] rabbit uterus, [c] human receptor : [2,3] recombinant human progesterone receptors A and B: [4] glucocorticoid receptor – [d] rat thymus, [e] rabbit thymus, [f] human receptor : [5] estrogen receptor – [g] rat uterus, [h] rabbit uterus, [j] human receptor : [6] androgen receptor – [k] rat prostate, [m] rat recombinant, [n] human receptor. * multiple determinations from several experiments

Ulipristal acetate has high affinity for the progesterone and glucocorticoid receptor. Weak and negligible affinity was shown for the androgen, estrogen and mineralocorticoid receptors respectively.

A receptor screen performed on 78 receptors showed some affinity of ulipristal acetate and its main metabolite for other receptors but a clinical relevance is unlikely. Binding affinities of the monodemethylated metabolite of ulipristal acetate for the progesterone and glucocorticoid receptors are similar to the parent compound.

In vitro studies have shown that ulipristal acetate is only a partial antagonist at the glucocorticoid receptor. The applicant describes that ulipristal acetate has agonistic activity at the PR-A isoform, and partial agonist/antagonist activity at the PR-B isoform. Although data about agonistic and antagonistic action are limited, *in vitro* results suggest that ulipristal acetate is a Selective Progesterone Receptor Modulator.

The *in vitro* progesterone antagonistic property of ulipristal acetate was confirmed *in vivo* were ulipristal acetate inhibited progesterone induced endometrial glandular proliferation in rabbits. No estrogenic or androgenic activity was noted by ulipristal acetate but a modest antiestrogenic and antiandrogenic activity was observed.

The antiovulatory and antifertility (post-coital) activity of ulipristal acetate has been investigated in rats in several studies. Ulipristal acetate has a dose-dependent antiovulatory effect and completely blocked ovulation at and above doses of 2 mg/kg. A partial blockade of ovulation was noted already at the lowest dose 0.5 mg/kg. The antifertility or post-coital effect was investigated in female rats that were mated with fertile males and dosed on day 4 to 6 of gestation. The animals were euthanized on day 10 of gestation and the number of concepti was recorded. Ulipristal acetate at doses of 2.0 mg/rat/day, either p.o. or s.c., prevented pregnancy in all animals in the respective groups while 1 mg/kg had a partial post-coital effect. In another dosing regimen with single 2 mg doses of ulipristal acetate to rats on different days of mating, no post-coital effect was observed on days 0, 1, 2 or 3 post-mating, but prevented 100% of gestations on day 4 but with less effect on day 5.

The applicant proposes several different mechanisms of action of the compound in humans:

- ability to block, disrupt or delay ovulation
- ability to block or delay ovulation even after the onset of the LH surge
- ability to delay maturation of the endometrium likely resulting in prevention of implantation

The Applicant's view that the lack of effectiveness of ulipristal acetate administered to rats as a single oral dose of 2 mg in the early days (0-3) after coitus does not preclude effectiveness of ulipristal acetate as an emergency contraceptive in humans is endorsed by the CHMP considering the differences in fertilisation process between rats and humans.

Administration of progesterone to ulipristal acetate treated pregnant rats reversed the post-coital antifertility effect and maintained pregnancy. It can therefore be concluded that the prevention of pregnancy was the consequence of progesterone antagonism. A dose-dependent post-coital effect of ulipristal acetate was observed in rabbits when the animals were dosed on gestation days 0-3. A compete block of gestation was seen at 10 mg/kg and a partial block of gestation at 4 and 8 mg/kg. On days 4, 5 or 6, 32 mg/kg, had no or slight post-coital effect while 64 mg/kg totally blocked gestation in the rabbit.

The ability of ulipristal acetate to terminate pregnancies was investigated in the guinea-pig and monkey. Ulipristal, mifepristone and lilopristone were approximately equipotent at the dose levels of 10 and 30 mg/day in terminating pregnancies in guinea-pigs when the animals were treated on days 43 and 44 of gestation. Pregnant long-tailed macaques (5/group) were administered ulipristal acetate 0.5 or 5 mg/kg/day p.o. or 0.5 mg/kg/day i.m. on days 23-26 of gestation. Pregnant animals were assessed by ultrasound pretreatment (day 23) and then monitored on days 26-28, 30, 32, 35, 55, 80, 100, 130 and 145. At 0.5 mg/kg of ulipristal acetate there was no loss of foetuses, while at 5 mg/kg 2/5 foetuses were lost. When using intramuscular administration of 0.5 mg/kg 4/5 foetuses were lost in ulipristal acetate treated animals. In monkeys in which pregnancy continued and which were allowed to deliver normally, there was no evidence of structural or physiological abnormalities in foetuses.

- Secondary pharmacodynamics

Anti-glucocorticoid activity.
Glucocorticoid activity as measured by adrenal function was investigated in rats. Administration of ulipristal acetate (62.5, 125, 250 mg/kg/day p.o. for 7 days) dose-relatedly increased adrenal weights. No effects were seen on pituitary weights or ACTH or corticosterone levels.

Androgenic/anti-androgenic activity.
Activity at the androgen receptor was studied in orchidectomised immature male rats.
In line with a weak affinity for the androgen receptor, ulipristal acetate showed a modest anti-androgenic effect (dose-dependent inhibition of testosterone induced increase in ventral prostate weight).

Effect of ulipristal acetate on cultured human uterine leiomyoma cells.
The effect of ulipristal acetate on cultured leiomyoma cells was investigated in two studies. Ulipristal acetate (10 nM-1 μM) inhibited the proliferation of viable cells by down-regulating proliferating nuclear cell antigen expression and inducing apoptosis by up-regulating cleaved caspase-3 and poly(ADP-ribose) polymerase expression; Bcl-2 expression, which is controlled in leiomyoma cells by progesterone, was down-regulated. Further studies in leiomyoma cells showed ulipristal acetate (10 nM-1μM) to reduce the expression of vascular endothelial growth factor (VEGF) and its receptors on cultured leimoyoma cells, but not on cultured normal endometrial cells; treatment with ulipristal acetate also altered the expression of progesterone isoform receptors (increased PR-A, decreased PR-B) in leiomyoma cells, but not in normal myometrial cells.
No proliferation was observed in a host of tumour cell lines during exposure to ulipristal acetate is reassuring, but does not rule out the possibility of increased progesterone induced proliferation due to the increased expression of PR. The Applicant was requested to further evaluate this aspect.
The data on leiomyoma cells only reports the expression profile after 48 hours of exposure. Study of the expression profiles of endometrial stromal cells using different exposure times, 8, 18 and 36 hours, suggests that expression of both PR isoforms is reduced after 18 hours of exposures, and increases after 36 hours of exposure. It is therefore likely that a relatively long exposure time is needed before PR expression is increased.

It is considered unlikely, after a single dose of Ellaone, that cells are exposed for an amount of time that is sufficient to induce increased expression of PR.

Effect of ulipristal acetate on endometrial stromal cells.
Treatment of cell cultures with 100 μM ulipristal acetate significantly inhibited estrogen and progesterone stimulated proliferation of endometrial stromal cells. Lower concentrations were without effect. Expression levels of AR, PR-A, PR-B, Fas and FasL were all increased in cells treated with ulipristal acetate, as were protein levels of AR, but not ERα or ERβ.

- Pharmacodynamics of metabolites

The pharmacodynamic activity of metabolites to ulipristal acetate was investigated in limited *in vitro* and *in vivo* studies. The main metabolites of ulipristal acetate, the mono-N-demethylated (CDB-3877) and di-N-demethylated (CDB-3963) were both found to be pharmacologically active, with CDB-3877 having the greater affinity at the progesterone receptor of similar magnitude as ulipristal acetate. *In vivo*, CDB-3877 inhibited endometrial proliferation after oral administration with lower magnitude of efficacy than ulipristal acetate while CDB-3963 was only weakly active.

- Safety pharmacology programme

Summary of safety pharmacology studies performed with ulipristal acetate. The studies were conducted according to GLP principles.

Organ System Evaluated **Study Number**	**Species/ Strain Gender/ Number/ Group**	**Method of Administration**	**Doses Duration**	**Comments/Results**
CENTRAL NERVOUS SYSTEM				
Functional observation battery (Irwin test),	Rat/SD 6F/group	po	5, 25, 125 mg/kg	No significant gross behavioural or physiological changes. The positive control chlorpromazine exerted its expected effect. **Conclusion:** Ulipristal acetate has no effect on behaviour or physiological changes.
CARDIOVASCULAR SYSTEM				
Action potential duration in Purkinje fibres	Dog/Beagle	*In vitro*	1, 3, 10 μM (0.475, 1.425, 4.75 μg/mL)	No effect on action potential duration or maximum rate of depolarisation. The positive control sotalol exerted its expected effect. **Conclusion:** Ulipristal acetate is unlikely to have an effect on cardiac sodium channels.
HERG tail current,	Transfected HEK293 cells	*In vitro*	10 μM (4.75 μg/mL)	No effect The positive control E-4031 exerted its expected effect. **Conclusion:** Ulipristal acetate had no effect on HERG tail current.
Cardiovascular effects (arterial blood pressure, heart rate and ECG) in conscious, telemetered female beagle dogs	Dog, Beagle 4 F/group	The animals were orally dosed sequentially with 7 days between doses of ulipristal acetate. Recordings were made for up to 24 hours after dosing.	5, 25, 125 mg/kg	5 mg/kg: the blood pressure was relatively unaffected 25 and 125 mg/kg: Increased arterial blood pressure (systolic, diastolic and mean), most marked at 25 mg/kg. Ulipristal acetate had no effect on heart rate or ECG at any dose. **Conclusion:** Ulipristal acetate significantly increased blood pressure. The NOAEL was 5 mg/kg. The exposure margin at NOAEL is slightly

				below clinical exposure (348 ng*h/ml divided by 548 ng*h/ml). The exposure margin at 25 mg/kg is 14 times the clinical exposure.
RESPIRATORY SYSTEM				
Respiratory parameters (respiratory rate and tidal volume) HRA2914-414	Rat/SD 8F/group	Plethysmography chambers	5, 25, 125 mg/kg po	No effect The positive control morphine exerted its expected effect. **Conclusion:** Ulipristal acetate had no effect on the respiratory parameters investigated.

Ulipristal acetate did not produce any unexpected or toxic effects in the safety pharmacology studies, which were conducted in accordance with ICH S7A and S7B. The only effect of relevance for humans is an increased arterial blood pressure observed in conscious female beagle dogs at 25 and 125 mg/kg, resulting in exposure margins of 14 and 133, respectively. The systemic exposure at NOAEL (5 mg/kg) is slightly below clinical exposure. Considering the proposed single dose administration to young individuals, the clinical relevance of the observed effect is assessed as low.

- Pharmacodynamic drug interactions

The applicant states that due to the wide range of products that might be taken simultaneously with ulipristal acetate, and due to the rapid decrease in relevant plasma levels, it is justified that no studies were performed. This was agreed by CHMP.

Pharmacokinetics

Methods
Assays for ulipristal acetate have been developed based on radioimmunoassay (RIA) and LC-MS/MS techniques. The RIA method relied on antisera raised in rabbits following sensitisation with ulipristal acetate 3-carboxymethyloxime and bovine serum albumin. The antiserum was shown to cross-react with the N-monodemethylated metabolite of ulipristal acetate (CDB-3877) for 76% and to a lesser degree with the N-didemethylated metabolite (CDB-3963) (59%). The RIA assay was used to support the initial pharmacokinetic studies and also the toxicokinetic analyses. LC-MS/MS methods were developed to support the safety pharmacology studies in rat and dog. No direct comparison between the RIA and LC-MS/MS methods can be performed, as the levels measured with the RIA assay are higher than using the LC-MS/MS method, because ulipristal acetate and two of its metabolites are measured with the RIA method versus ulipristal acetate alone with the LC-MS/MS method. In addition, the comparison between the two analysis methods is not possible, because the unit of the RIA method is pg/tube and with the LC-MS/MS method ng/ml.

Summary of pharmacokinetics for ulipristal acetate

Absorption	Rapidly and well absorbed after oral administration to mice, rats, rabbits, dogs and monkeys. C_{max} = 1 h in rats, 1-2 hours in dogs and 4 h in monkeys following oral administration.
Bioavailability	Rats approximately 80%. Monkeys approximately 112%. Human: No data
Dose proportionality	The exposure appeared to be less than proportional over the dose range 5 to 125 mg/kg for both ulipristal acetate and the metabolite CDB-3877 in rats but the converse was seen in dogs. When analysed by RIA, exposure of rats and rabbits increased less than proportionally over the dose range 50-1250 mg/kg. Non-linear kinetics in humans, with less than dose proportional increase in exposure.

Terminal plasma half-life	Rat: 6 hrs following oral administration Monkey: 87 hrs following oral administration Human: 32 hours after oral administration
Distribution	Highly protein bound (96.7-99.5%) to plasma proteins of mouse, rat, rabbit, dog, monkey and human. ^{14}C-ulipristal was widely distributed in rats and monkeys. Higher concentrations of radioactivity were seen in pigmented tissues (uveal tract, pigmented skin and meninges). No human data on excretion into milk. No information on distribution over placenta.
Metabolism	Rapid and extensive metabolism possibly via cytochrome P450 (CYP3A4). A large number of metabolites are produced, up to 28 in rat and 20 in monkeys. *In vivo* metabolism data in humans are very limited.
Excretion	Rats and monkey: main route via faeces (83.3-44.7%). Biliary excretion was observed in the rats. Human: poorly characterised (no human mass balance study available), main elimination route likely via metabolism.

Absorption
Ulipristal acetate was rapidly and well absorbed after oral administration to mice, rats, rabbits, dogs and monkeys. Following oral administration of 5 mg/kg of ^{14}C-ulipristal acetate to rats and monkeys Cmax was observed at 1 and 4 hours, respectively, after dosing. Results obtained by LC-MS/MS following oral dosing to rats and dogs at dose levels of 5, 25 and 125 mg/kg confirmed the rapid absorption (T_{max} of 1-5 hours in rats, 1-2 hours in dogs). Despite very limited data and differences in analysis techniques, it appears that the Cmax and AUC are approximately dose proportional.

Comparisons of exposure after intravenous and oral administration gave bioavailability figures of 80 and 113% in rats and monkeys, respectively. Studies in monkeys with assay by RIA confirmed the good bioavailability. The applicant showed that different oral formulation influenced the bioavailability ulipristal acetate in monkey. In addition, data in rat showed that the feeding status of the animal influenced the bioavailability of ulipristal acetate, with a lower bioavailability in fed animals than in fasted animals. This is in agreement with the statement of the applicant that the absorption of ulipristal acetate is pH-dependent and may be reduced in situations where gastric pH is increased irrespective of cause.

Distribution
Ulipristal acetate was highly bound (96.7-99.5%) to plasma proteins of mouse, rat, rabbit, dog, monkey and human; studies with human protein fractions showed a major role of α1-acid glycoprotein. In addition, ulipristal acetate is also highly bound in blood (4.86% to blood cells and 94.09% to plasma proteins).

Following intravenous and oral administration of ^{14}C-ulipristal acetate to rats and monkeys, radioactivity was widely distributed. In rats, concentrations of radioactivity declined after peak levels, but quantifiable radioactivity levels were still present in all tissues at the final sampling time of 3 days. In addition, in monkeys even after 14 days radioactivity was measurable in all investigated tissues. The liver accounted for the majority of radioactivity in the tissues in the distribution studies in rat and monkey. However, ulipristal acetate also showed a high tissue to plasma ratio in the kidney, clitoris, ovary, uterus, adrenal, fat, uveal tract, pigmented skin and mucosa of the gastro-intestinal tract, indicating accumulation in these organs if the drug is used again a month later. Most likely this has no implications, because ulipristal acetate is given as a single dose, but in repeated dose this could result in toxicity due to accumulation.

Metabolism
Metabolism of ulipristal acetate was investigated *in vitro* in liver microsomal preparations from mice, rats, rabbits, dogs, monkeys and humans. All species produced the same two major metabolites, but the proportions varied between species. Some minor metabolites were detected in the animal species which were not detected with human microsomes. No metabolites were detected that were unique to

humans. The *in vivo* metabolism data in humans are very limited. The active metabolite 3877A has been measured; however, no human mass balance study is available.

In studies with Supersome™, the metabolism of ulipristal acetate was predominantly mediated by CYP3A4, and to a small extent by CYP1A2 and CYP2D6. Pharmacokinetic interaction studies *in vitro* examined the potential for ulipristal acetate to inhibit a range of CYP isozymes. Ulipristal acetate did not inhibit marker enzyme activities for CYP1A2, CYP2C19 or CYP2E1 at any concentration evaluated. Inhibition of CYP2C9, CYP2D6 and CYP3A4 activity was observed only at the highest concentration (100 µM, 47.56 µg/mL) although the extent of this inhibition is indicative of very weak inhibitors. Concomitant administration of ulipristal acetate with potent CYP3A4 inhibitors (*e.g.* ketoconazole, itraconazole, ritonavir, telithromycin, clarithromycin, nefazodone) may inhibit the metabolism of ulipristal acetate and cause increased plasma levels. In addition, concomitant administration with potent CYP3A4 inducers (*e.g.* rifampicin, phenytoin, phenobarbital, carbamazepine, *Hypericum perforatum*/St John's wort) may reduce plasma concentrations of ulipristal acetate and may result in decrease in efficacy.

Excretion
Studies examining plasma, urine, faeces and, in rats only, bile after oral and intravenous administration to rats and monkeys identified a large number of metabolites – up to 28 in rat and 20 in monkeys. Following administration of ^{14}C-ulipristal acetate to rats and monkeys, excretion of radioactivity was predominantly faecal. After oral dosing of 5 mg/kg, faeces accounted for 83.3% of the administered radioactivity and urine 2.4%; corresponding figures for the monkey were 44.7 and 6.3% (total recovery of radioactivity was much lower in the monkey, 69.7%, as compared to the rat, 93.2%). In bile duct cannulated rats, bile accounted for 61.5% of the administered dose with a further 28.8 and 4.0% found in faeces and urine, respectively.

Toxicology

- Single dose toxicity

In single dose toxicity studies, only one dose of ulipristal acetate (1250 mg/kg) was investigated in rats and rabbits, which was far in excess of the human dose (140-fold and 197-fold based on Cmax values for rats and rabbits respectively). The apparent LD50 was <1250 mg/kg in the rat and >1250 mg/kg in the rabbit. Although more dose levels were used in the repeat dose toxicity studies, single dose administration is the more appropriate dosing scheme for this indication. More dose levels should have been investigated to allow assessment of any risks relevant for humans. However, due to the fact that no unexpected toxicity was evident in the repeat dose studies, no further single dose toxicity studies are required.

- Repeat dose toxicity (with toxicokinetics)

The pivotal repeated-dose toxicity studies are considered to be the 6-month studies in the rat and cynomolgus monkey. These are supported by 14-day preliminary studies in the rat and rhesus monkey. Toxicokinetic measures were included in all studies. There was no investigation of recovery following cessation of dosing in any of these studies. Dosing was oral with ulipristal acetate suspended in ASV: 0.9% sodium chloride, 0.4% polysorbate 80, 0.5% carboxymethylcellulose and 0.9% benzyl alcohol in distilled or deionised water.

Administration of ulipristal acetate (1, 5 and 25 mg/kg/day) to rats in the 6-month toxicity study caused changes in haematological (increased white cell, lymphocyte and neutrophils; reduced erythrocyte numbers, haematocrit and haemoglobin) and biochemical (reduced sodium, chloride; increased globulin, total protein and cholesterol) parameters. Organ weight analysis showed increased liver and adrenal weights and decreased ovaries, uterus and thyroid weights at the 5 and 25 mg/kg/day dose levels. On histological examination, these correlated with adrenal cortical and liver hepatocyte hypertrophy, ovarian follicular cysts and follicular atresia and uterine glandular dilation: pituitary hyperplasia and mammary galactoceles were also noted. These histological changes were most notable

in animals treated with 5 or 25 mg/kg/day but the changes in mammary glands and ovaries were also seen at 1 mg/kg/day. There was a significant positive correlation between pituitary weights and serum prolactin levels and between adrenal weights and serum corticosterone levels. Treatment-related changes were seen at all dose levels and it was not possible to determine a NOEL in this study.

The 14-day study in rhesus monkeys had only two dose levels, 20 and 100 mg/kg/day. Two animals in the high-dose group were particularly affected by treatment with one animal euthanized on day 8. No treatment-related changes in haematology parameters were observed while high-dose animals showed changes in some biochemistry parameters which are considered of low clinical relevance. Serum cortisol levels showed a general trend of increasing values in the high-dose group. Organ weights were increased in the high-dose group for liver, thyroid and heart and, for animals in both treated groups, in the spleen, adrenals, ovaries and kidneys. A dose related increase in mucous cells in the cervix in low- and high-dose groups and a decreased bone marrow cellularity in two high-dose animals were observed at histopathology.

The 6-month study in cynomolgus monkeys was conducted at dose levels of 1, 5 and 25 mg/kg/day. Administration of ulipristal acetate disrupted the hypothalamic-pituitary-adrenal axis with increased cortisol and prolactin levels. Although hormone levels were altered at all dose levels, the consequences were most apparent at the 5 and 25 mg/kg/day dose levels. The menstrual cycle was disrupted in mid- and high-dose animals with some high-dose animals being acyclic throughout the study. Lymphocyte numbers were reduced and neutrophil numbers increased at these dose levels; this might be expected as a consequence of the increased circulating cortisol levels resulting from disruption of the feedback mechanisms controlling the release of ACTH. Adrenal weights were increased in high-dose animals (there was a significant correlation between adrenal weights and serum cortisol levels), consistent with the hypertrophy observed at histology; although thymus weights were decreased at this dose level, there were no histological correlates. Histology also showed cystic dilatation of uterine endometrial glands in mid- and high-dose animals, with one high-dose animal showing mild squamous metaplasia.

Apart from the effects on the liver, which might be due to increased metabolic load, all effects have been seen after long-term treatment with other hormones, and can be explained by an exaggerated pharmacodynamic effect.

- Genotoxicity

The standard genotoxicity battery was performed and results were negative. The doses used in the main *in vivo* micronucleus test were determined from the results from adequate dose range finding studies. In vivo exposure in the mouse micronucleus study has been confirmed by radioactivity.
There is no evidence of genotoxic potential of ulipristal acetate.

- Carcinogenicity

No long-term carcinogenicity studies have been performed. Ulipristal acetate is used as a single dose, and carcinogenicity testing is therefore considered not necessary.

- Reproduction Toxicity

The programme of reproductive and developmental toxicity studies conducted with ulipristal acetate have focused on embryofoetal development using standard dosing periods in rats and rabbits and possible effects on pups from dams which were dosed during the early days of pregnancy. Doses in these studies were low so as to provide data at levels which did not impair pregnancy. There were no toxicokinetic measures incorporated into these reproductive and developmental toxicity studies. The studies were according to the Applicant not intended to provide safety margins in terms of exposure, but to give data to guide on the consequences of ulipristal acetate administration at dose levels which allowed pregnancies to continue.

Reproductive and developmental studies performed with ulipristal acetate.

Study type/ Study ID GLP	Species/ Number/ Sex/group	Route/ dose (mg/kg)	Dosing period
Male fertility study GLP: no	Rat/SD, Males, 6-8 animals/ group	0, 10 po	M: 14, 35 or 70 days premating
Preliminary embryofoetal study in rats	Rat/SD Females, 5/group	0, 0.1, 0.3, 1, 3, 10 po	F: G6-G15
Embryofoetal study in rats	Rat/SD Females, 25/group	0, 0.1, 0.3, 1 po	F: G6-G17
Embryofoetal study in rabbits	Rabbit/NZW Females, 20/group	0, 0.1, 0.3, 1	F: G6-G18
Pre/post-natal development GLP: no	Rat/SD Females, 10/group	0, 0.5, 1 mg/rat po	F: G0-G3
Late gestational effect GLP: no	Rat/SD Females, 10/group	0, 2, 4, 8 mg/rat	F: G17-G19

* G – gestation day

Ulipristal acetate has no effect on male fertility.

As expected, ulipristal acetate is embryotoxic at low doses, when given to rats and rabbits in repeated doses at gestation days 6-17 or 6-18 respectively. Considering the pharmacodynamics of the product and the indication applied for, the most important effects to consider are those in live foetuses, and the applicant has chosen a dose in the embryo/foetal studies that allows sufficient foetuses to survive for examination. In rats and rabbits, no effects in live foetuses were observed at doses up to 1 mg/kg/day in the pivotal studies.

In the pup development study, effects on fertility and litter size are as expected. Equal to the embryo-foetal development studies, considering the pharmacodynamics of the product and the indication applied for, the most important effects to consider are those in surviving offspring. When dosed at GD0-3 with up to 4 mg/kg/day, no effects were observed in the offspring of rats. Apart from the study in macaques where no effects on surviving offspring were evident after dosing on days 23-26, other robust data on surviving offspring of animals dosed after GD-3 is not available. It has not been possible to evaluate the teratogenic potential of ulipristal acetate since the doses are low in order to maintain gestation of the animals.
The applicant has committed to perform a pre- and postnatal development study. The results of this study are awaited to assess the effects of possible off-label use after the first 5 days post-coital.

- Toxicokinetic data

Toxicokinetic measures were included in all studies. These were often minimal in terms of sampling times but they did serve to substantiate the exposure of the animals to ulipristal acetate and allow some comparisons to be made to the exposure levels reached in clinical use of ulipristal acetate.

There are deficiencies in the toxicokinetic documentation with different assay methodologies used (RIA in animals, LC-MS/MS in humans) which hampers an comparison between animals and humans. In the rat, no exposure margin exists while in the pivotal 6 month toxicity study in the Cynomolgus monkey, an exposure margin above clinical exposure was obtained. The toxicokinetic documentation was however accepted considering that the obtained toxicity findings can be explained by an exaggerated pharmacodynamic effect of ulipristal and the proposed single dose administration of ulipristal.

Overview of the toxicokinetic data in studies performed with ulipristal.

Study ID/ GLP	Species Sex/ No/ Group	Dose/Route mg/kg/ day	Dura-tion	NOEL mg/kg/ day	Major findings/comments
HRA 2914-433 GLP	SD rat, females, 10/group	0, 4, 20, 100 oral gavage	14 days	NOEL: 4 mg/kg	Analysis of serum levels of ulipristal and immunoreactive metabolites in samples obtained approximately 24 hours after the final dose gave levels of 7.0±2.1, 47.0±9.6 and 150.3±47.0 ng/mL at 4, 20 and 100 mg/kg/day, respectively.
HRA 2914-435 GLP	SD rat females, 20/group	0, 1, 5, 25 oral gavage	6 months	NOAEL: could not be deter-mined	Serum levels of ulipristal and its immunoreactive metabolites in samples obtained at necropsy were 11.2±0.7, 75.8±4.9 and 147.3±9.5 ng/mL at 1, 5 and 25 mg/kg/day, respectively.
HRA 2914-434 GLP no	Rhesus macaques 4 females/gro up	0, 20, 100 oral gavage	14 days	NOAEL: could not be deter-mined	Serum levels of ulipristal and immunoreactive metabolites were determined in samples taken each day before dosing. At the 20 mg/kg/day dose level, mean values ranged from 122±47 to 354±80 ng/mL, with the range at 100 mg/kg/day being 525±219 to 2384±918 ng/mL.
HRA 2914-436 GLP	Cyno-molgus monkey 4 females/gro up	0, 1, 5, 25 oral gavage	6 months	NOAEL: 1 mg/kg	Samples for analysis of ulipristal and immunoreactive metabolites were obtained approximately 4 hours after dosing, as were those for analysis of cortisol and prolactin: AUC0-180days values for ulipristal and immunoreactive metabolites were 14861±1073, 124702±13266 and 492775±32478 ng.day/mL for the 1, 5 and 25 mg/kg/day groups respectively.

- Local tolerance

n/a

- Other toxicity studies

An evaluation of the *in vitro* phototoxicity of ulipristal acetate (2.5-30 µg/mL) on Balb/c 3T3 fibroblasts using the neutral red uptake assay has been performed (study HRA2914-448). The highest concentration of ulipristal acetate used was limited by solubility. When tested up to the limit of solubility, ulipristal acetate was not phototoxic.

No other toxicity studies have been performed.

Ecotoxicity/environmental risk assessment

A Phase I ERA based on the CHMP Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00) adopted by CHMP on 01 June 2006 was provided.

The Applicant concluded that the calculated concentration for $PEC_{Surface\ water}$ is less than the 0.01 µg/L threshold value given in the CHMP guideline, and that the release into the environment of ulipristal acetate following the prescribed use of Ellaone is unlikely to represent a risk for the environment. This was not accepted by CHMP because ulipristal acetate is a selective progesterone receptor modulator with the potential to affect the reproductive outcome in many species, making the action limit of 0.01 µg/L potentially not applicable. A phase II environmental risk assessment was requested, which the applicant has committed to perform. A tailored risk assessment strategy should be followed that addresses the specific mechanism of action.

Discussion on the non-clinical aspects

In vivo pharmacology results show that ulipristal acetate has antiprogesterone activity shown as inhibition of progesterone induced endometrial glandular proliferation in the anti-McGinty and anti-Clauberg tests. The monodemethylated metabolite has modest activity in the anti-Clauberg test. Ulipristal acetate seems most potent after oral administration. The modest antiuterotropic effect observed in rats is most likely due to anti-progestational activity through the progesterone receptor, since ulipristal acetate has no affinity for the estrogen receptor. An anti-estrogen effect of ulipristal acetate is therefore highly unlikely.

Ulipristal acetate was shown to be effective in inhibiting ovulation and preventing pregnancy in rats. When given to guinea pigs and macaques at later stages of pregnancy, ulipristal acetate terminated gestation in some animals. However, these endpoints are not relevant for the current indication applied for. The most relevant dosing scheme in relation to a clinical setting, is a single administration on the first few days post-coital. In rats, efficacy was only shown for dosing after day 4. In rabbits single doses were only investigated after day 4, in which a high dose was necessary to achieve a reduction on pregnancy rates. Pre-clinical efficacy at days 0-3 using single dose has not been shown, presumably due to differences in fertilisation process between preclinical species and humans.

Pharmacodynamic studies performed *in vivo,* and reproduction toxicity studies, clearly demonstrated that repeated doses above 1 mg/kg to rats and rabbits cause embryolethality. Doses below 1 mg/kg are so low that malformations/variations are difficult to investigate in the animal species. There are data in rats and monkeys which indicate no adverse effect of ulipristal acetate when the embryo/foetus is exposed during early gestation, however, due to a small number of animals and low doses used, no conclusion for human safety could be drawn from these studies.

The CHMP requested additional information on human in vivo metabolism data due to the need to assess the relevance of the animal species used in reproduction toxicity studies. It was agreed that for this indication with only single dose administration on single occasions, the requirements for human pharmacokinetic data may be lowered compared with a product intended for chronic administration.

The main safety concern with ulipristal acetate at the proposed therapeutic use is the potential adverse effects on an embryo that develops to term due to a failed emergency contraception. The applicant was asked to summarise all available data and include a discussion on exposure margins at the tested doses.
It can be concluded that, due to hormonal differences, the rodent species are probably less relevant. Focus was therefore on data in primates which was summarised in the SPC section 5.3.

The safety concerns relating to an embryolethal and teratogenic potential of ulipristal acetate are therefore considered addressed with appropriate changes to the SPC.

2.4. Clinical aspects

Introduction

Ellaone contains ulipristal acetate, a synthetic selective progesterone receptor modulator with antagonistic and partial agonistic effects, as claimed by the applicant, at the progesterone receptor. An effective emergency contraceptive method has the potential to help out women, who might otherwise have become pregnant, thereby possibly reducing the need for abortion.

Currently, the standard of care for emergency contraception is the administration of 1.5 mg of levonorgestrel within 72 hours of unprotected intercourse.
It should be noted that levonorgestrel is only registered for the time frame of 0-72 hours, as there is limited evidence of efficacy after 72 hours after UPI. Longer duration of efficacy, beyond the approved margin of levonorgestrel would be an advantage.

Normal sperm can survive in the female reproductive tract and retain the ability to fertilize an egg for at least 3 and up to 5 days, but an oocyte can be successfully fertilized for only approximately 12-24 hours after it is released.[4] Although not specifically stated it is assumed that for this reason several published emergency contraception studies in women are conducted up to maximally 120 hours after UPI.[5]

[4] Wilcox AJ, Weinberg CR and Baird DD Post-ovulatory ageing of the human oocyte and embryo failure. Hum Reprod 1998;13:394-397.
[5] Cheng L, Gülmezoglu AM, Piaggio G, et al. Interventions for emergency contraception. Cochrane Database Syst Rev. 2008;2:CD001324.

This submission is based on six phase I studies conducted to determine the pharmacodynamic and pharmacokinetic properties of ulipristal acetate and three efficacy and safety studies. The National Institute of Child Health and Human Development (NICHD) initiated the clinical development phase for use as an emergency contraception. The applicant, HRA Pharma, licensed the rights to the compound in 2000. For this reason, data for three out of four pharmacodynamic studies are only available as publication.

The efficacy and safety studies submitted in support of the emergency contraception indication were two pivotal phase-II multicenter, double-blind, active-controlled clinical studies and one pivotal phase-III uncontrolled study, as shown in the table below.

Tabular listing of the efficacy and safety studies.

Study ID	**No. of study centres / locations**	**Design**	**Study Posology**	**Study Objective**	**Subjs by arm enrolled/ mITT**	**Duration**	**Mean age; Race**	**Diagnosis Incl. criteria**	**Primary Endpoint**
HRA2914-507	7 sites in the US, September, 20 2003	Prospective, randomized, double-blind, multicenter, active-controlled **(Phase II)**	ulipristal acetate 50 mg unmicronized in gelatin capsule **(taken up to 72h of UPI)** Levonorgestrel 2 x 0.75 mg 12 hours apart Oral	To study the efficacy, safety and tolerance in comparison to levonorgestrel for emergency contraception	1,672 832/792 (ulipristal acetate) 840/786 (levonorgestrel)	Single dose	24.3 years, white (73%), black or African American (15%)	Healthy women requesting emergency contraception within 72h after intercourse/group	Comparison of post-treatment pregnancy rates
HRA2914-508	9 sites in the US, August, 20 2001	Prospective, randomized, double-blind, multicenter, active-controlled **(Phase II)**	ulipristal acetate 50 mg unmicronized in gelatin capsule 10 mg micronized in gelatin capsule **(taken up to 72h of UPI)** Oral	To study the efficacy, safety and tolerance of two different doses for emergency contraception	400	Single dose	24.4 years, Caucasian (69.5%), black or African American (17.9%)	Healthy women requesting emergency contraception within 72h after intercourse/group	Comparison of post-treatment pregnancy rates for the Efficacy Evaluable (EE) population
HRA2914-509	40 sites in the US, November 27, 2006 – March 31, 2008	Prospective, uncontrolled, single arm, multicenter **(Phase III)**	ulipristal acetate 30 mg micronized in tablet (**taken between 48h and 120h of UPI**) Oral	To study the efficacy, safety and tolerance of a single dose for emergency contraception	1533 Treated 1241 (mITT)	Single dose	24.4 years, white (60%), black or African American (22%)	Women aged 18 years of age or older enrolled for emergency contraception	Pregnancy rate (%) was the primary efficacy parameter

Currently, there is an ongoing double-blind, active-controlled phase III study (**HRA2914-513**), conducted by HRA Pharma, which compares 30 mg micronized ulipristal acetate with 1.5 mg levonorgestrel. The protocol calls for inclusion of 2,000 subjects in this study and the study report will be submitted by July 2009.

Paediatric Investigation Plan (PIP)

The applicant has submitted a PIP to the EMEA on 24 July 2008 (EMEA-000305-PIP-01). The EMEA Paediatric Committee in its meeting of 4-6 March 2009 adopted a positive opinion on this PIP, agreeing the following clinical studies:

- Single-blind, multicentre, randomized, parallel group safety and efficacy study of ulipristal acetate 30 mg versus levonorgestrel 1.5 mg for emergency contraception within 120 hours of unprotected intercourse, in adolescents (and in adults).
- Open-label, observational safety study of ulipristal acetate for emergency contraception within 120 hours of unprotected intercourse, in adolescents (and in adults).

The opinion of the Paediatric Committee also included certain measures to monitor safety, including follow-up of any pregnancy, occurring in treated patients, until delivery or termination, and a study in rats from day 6 of gestation to day 21 of lactation.

GCP

The clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Pharmacokinetics

The pharmacokinetic information submitted by the applicant is limited. Only two studies and one article with respect to the pharmacokinetics of ulipristal acetate were submitted by the applicant (HRA2914-501, HRA2914-503 and HRA2914-504).

Two analytical methods were used. Firstly, a RIA method was used that was not specific for the parent compound alone. Also the metabolites did show a cross reaction with this method. Secondly, a LC-MS/MS method was developed, which could determine both the parent compound and the main metabolite (3877A) in human plasma.

- Absorption

The applicant did not investigate the absolute bioavailability of ulipristal acetate in humans nor was it discussed in the clinical overview in the initially submitted dossier. Therefore the extent of absorption of ulipristal acetate was not known. The applicant was requested to give a justification for not conducting an absolute bioavailability study and to provide information on the extent of absorption of ulipristal acetate.

The CHMP concluded that the plasma levels of ulipristal acetate reached with the 30 mg to-be-marketed micronised tablet formulation should approximate those achieved with the 50 mg crystalline capsule evaluated in the Phase II program and allow extrapolation of the safety and efficacy results from the two Phase II studies (HRA2914-507 and HRA2914-508).

With respect to the influence of food on bioavailability, a study submitted in the answers to the day 120 report investigated absorption of ulipristal acetate from the commercial 30 mg Ellaone tablet in the fasting state and after a high-fat meal. It was shown that there was no dramatic effect of food on the exposure of ulipristal acetate and its active metabolite. Mean C_{max} of ulipristal acetate was decreased by approximately 44%, median Tmax was delayed from 0.75 to 3 hours and $AUC_{0-\infty}$ was increased by approximately 26%. Similar results were observed for the active metabolite 3877A, with about 38% decrease in C_{max} and 20% increase in AUC.

In the clinical studies, there were no food restrictions, as patients were dosed as soon as possible when they came to the study site and were in need of emergency contraception. Analyses of results based on subjects who had reported food intake within 2 hours before treatment vs. the overall study population were presented. Based on a small amount of data, no difference in pregnancy rate was observed between those groups, although the confidence interval was wide.

The applicant concluded that the recommendation in section 4.2 should be that Ellaone can be administered with or without food. The modest increase in AUC is not likely to be a safety concern. The decrease in C_{max} was relatively large, though. The mechanism of action of ulipristal acetate in the prevention of pregnancy is not completely elucidated, i.e. it is unknown whether the effect is dependent on reaching a certain threshold concentration or if the total exposure is of greater importance. The clinical relevance of the observed food effect is difficult to exactly predict. C_{max} is decreased while the overall systemic exposure is somewhat higher in the fed state. However, since Ellaone was administered regardless of previous food intake in the clinical study and since it is of

importance that Ellaone is administered as soon as possible after an unprotected intercourse, the recommendation proposed by the applicant was endorsed by CHMP.

- Distribution

Ulipristal acetate is mainly bound to plasma proteins (99%). The volume of distribution was not estimated. Results from a single-dose pharmacokinetic study HRA2914-504 show that plasma levels of ulipristal acetate and its metabolite achieve peak concentrations less than one hour after intake and decrease rapidly thereafter. At 12h after intake, concentrations decrease to well below 5% of peak concentrations.

In the absence of specific data on the distribution of ulipristal acetate into milk, initial guidance for clinical recommendations can be drawn from the plasma pharmacokinetic profile. Therefore, in the SPC it is stated that "It is unknown whether ulipristal acetate is excreted in human or animal breast milk. Ulipristal acetate is a lipophilic compound and may theoretically be excreted in breast milk. A risk to the breast-fed child cannot be excluded. After intake of Ellaone breastfeeding is not recommended for at least 36 hours".

Additionally, results of ulipristal acetate transfer into milk in the rat peri-postnatal study are awaited. Furthermore, pending confirmation on this study the applicant also committed to conduct a study investigating the pharmacokinetics of ulipristal acetate in healthy breastfeeding women who take 30mg and the amount of drug transferred into human milk, similar to the design of the study published for levonorgestrel (Gainer et al, 2007). If necessary, the applicant will propose a variation to update the SPC once the results are available.

- Elimination

The half life of ulipristal acetate is approximately 32h and the Cl/F 77l/h.

In preclinical studies in rats and monkey's after administration of radiolabeled drugs intravenously the main route of excretion was the faeces and only a minor part (< 10%) was excreted in urine.

In vitro studies show that the metabolism of ulipristal acetate is mediated by mainly CYP3A4 and two metabolites are formed. Only one metabolite is analyzed in plasma samples of the pharmacokinetic studies. Lack of information related to interactions and special populations (i.e. patients with renal or hepatic impairment) was dealt with appropriate information in the SPC, for instance not recommending the use of Ellaone in patients treated with CYP3A4 inhibitors or inducers.

- Dose proportionality and time dependencies

The issue of linearity and comparability between the micronised/unmicronised formulation is discussed in the Absorption section.

The lack of formal dose proportionality studies is considered acceptable as only one strength is applied for.

As the product is only administered once, time dependency of the pharmacokinetics is considered not applicable for this product.

- Special populations

From the preclinical studies it can be concluded that the excretion in urine is less than 10% of the absorbed dose. Therefore, renal impairment will therefore probably not influence the exposure to ulipristal acetate in a clinical significant way.

Ulipristal acetate is metabolised by cytochrome P450 co-enzymes in the liver. Therefore, liver impairment can influence the pharmacokinetics of ulipristal acetate in a significant way. However, as

Ellaone is administered only once and most likely to healthy young females liver impairment will probably not influence the efficacy and safety of ulipristal acetate in a clinically significant way.

Regarding the administration to adolescents, please refer to the section on the paediatric investigation plan (PIP).

- Pharmacokinetic interaction studies

No interaction studies were submitted and in the SPC is only mentioned that potent CYP3A4 inhibitors may increase the exposure and inducers may reduce plasma concentrations of ulipristal acetate. However, interactions with other medicinal products may influence the efficacy of this product, especially if the product is administered with a CYP3A4 inducer. This was addressed in the SPC with a warning regarding concomitant contraceptive use and the need of additional barrier contraceptive methods until the following period.

Pharmacodynamics

- Mechanism of action

Ulipristal acetate is a synthetic Selective Progesterone Receptor Modulator (SPRM). *In vitro*, Ulipristal acetate binds competitively to the progesterone, glucocorticoid and androgen receptors, but has minimal affinity for the estrogen or mineralocorticoid receptors. Pre-clinical studies indicate that ulipristal acetate binds to the human progesterone, glucocorticoid and androgen receptors at approximately 6, 1.5 and 0.2 times the affinity of the endogenous ligands.
The compound has antiprogestational activity in rats, rabbits and monkeys, with additional antiglucocorticoid and antiandrogen activity at doses ~50 times higher than those needed for antiprogestational activity. Since progesterone is critical for implantation, it was thought that ulipristal acetate may have promise as a contraceptive agent.

- Primary and Secondary pharmacology

Single-dose studies

Three single-dose pharmacodynamic studies were performed with unmicronized ulipristal acetate in support of the indication by assessing the effect on endometrial maturation and the inhibition of ovulation in the mid-luteal phase (**HRA2914-503**), mid-follicular phase (**HRA2914-505**) and early-luteal phase (**HRA2914-506**). All studies were carried out in women, who agreed to use mechanical or sterilization methods of contraception throughout the study.

- Mid-luteal administration of ulipristal acetate resulted in early endometrial bleeding, indicating a direct action on the endometrium. Despite the small number of women, the study clearly showed that a dose of 200 mg is too high, due to the side effects of prolonged bleeding (two women had a dramatic increase in length of bleeding of 15 and 20 days). The 200 mg dose was omitted from **HRA2914-505** and **HRA2914-506**.
- At mid-follicular phase, doses of 10-100 mg ulipristal acetate caused a suppression of growth of the lead follicle and subsequent delay in ovulation that was greatest at the highest doses (50 and 100 mg), but inhibited luteal phase endometrial maturation similarly at all doses. The threshold for altering endometrial morphology thus appears lower than for inhibition of ovulation.
- At early-luteal phase, none of the given doses (10, 50 and 100 mg) affected the length of the follicular, luteal or overall cycle length during the baseline, treatment or post-treatment menstrual cycle. A significant delay in endometrial maturation occurred in the 50 and 100 mg groups compared to the placebo and 10 mg groups (p=0.02).

The dose of 50 mg unmicronized ulipristal acetate was chosen in the phase II studies, since this was the minimal dose that alters endometrial maturation and induces inhibition of ovulation.

Since the single-dose studies were performed by the NICHD and data were only available from the publications, limited data are available regarding the adverse effects. Ulipristal acetate at 10-50 mg appears to be well tolerated. Post-treatment cycle characteristics were comparable to baseline. The side effects nausea, headache and abdominal pain were noted during 12-weeks administration (**HRA2914-510**), but no mention is made of these side effects after single-dose administration.

Furthermore, a dose-response relation was observed between the ulipristal acetate dose and the presence of cysts in the single-dose **HRA2914-505** study and the multiple-dose **HRA2914-510** study. It is important to know whether these cysts disappear after single-dose administration. In the majority of the subjects this was the case, but not in all women and some women even required surgery. This is discussed further in the Safety section.

Pharmacodynamic interactions with other medicinal products or substances were not studied.

In conclusion, the mechanism of action, as claimed in 5.1 of the SPC *"The primary mechanism of action is thought to be inhibition or delay of ovulation, but alterations to the endometrium may also contribute to the efficacy of the product",* is sufficiently documented.

Clinical efficacy

- Dose response studies

Dose selection The 50 mg unmicronized ulipristal acetate dose selected for both phase II studies (**HRA2914-507** and **HRA2914-508**) was based on the aforementioned pharmacodynamic studies.

Design and results Two phase II studies evaluated the safety and efficacy of ulipristal acetate for emergency contraception when taken 0-72h after UPI.

The **HRA2914-507** study was designed as a non-inferiority trial to test the hypothesis that 50 mg unmicronized ulipristal acetate has a pregnancy rate no worse than that of 2 x 0.75 mg levonorgestrel with a noninferiority margin (δ) of 2%. At the 2.5% level of significance (upper limit of the 95% confidence interval), a sample size of 770 subjects in each treatment group was sufficient to reject with 80% statistical power the null hypothesis. For the mITT population, the pregnancy rate in ulipristal acetate group was 1.52% (0.785-2.632). This trial demonstrated that 50 mg unmicronized ulipristal acetate was at least as effective as levonorgestrel as an emergency contraceptive (-0.27, 95% CI -1.992, 1.420 for the mITT population), as the upper limit of the 95% confidence interval was below 2%. The pregnancy rate and prevented fraction for the EE population administered ulipristal acetate were, respectively, 0.91% (0.365-1.857) and 85% (68-93).

The **HRA2914-508** study was also set up as a non-inferiority trial with a margin (δ) of 2.5%. The data showed that 10 mg micronized ulipristal acetate was inferior to 50 mg unmicronized ulipristal acetate at preventing pregnancy (1.44, 95% CI -0.660, 3.820). The upper limit of the 95% CI of the pregnancy rate (2.74%) of 10 mg micronized ulipristal acetate was beyond the clinically unacceptable threshold of 4%, i.e. 4.985%. The pregnancy rate and prevented fraction for the EE population administered 50 mg ulipristal acetate were respectively 1.30% (0.423-3.016) and 76.19% (52.83-91.78). For 10 mg micronized ulipristal acetate the prevented fraction was 52.38% (29.78-74.29).

- Main study**: Study HRA2914-509**

This Phase III, prospective, open-label, single-arm study, conducted in 45 centres in the United States, was performed in order to evaluate the efficacy, safety and tolerability of 30 mg micronized ulipristal acetate for emergency contraception when taken between 48 and 120 hours after unprotected intercourse. As no emergency contraceptive is registered for more than 72 hours after UPI, no active-controlled study was performed.

METHODS

Study Participants

Women (aged ≥18 years), with regular menstrual cycles (between 24 and 35 days and intra-individual variations less than or equal to 5 days), requesting emergency contraception between 48 and 120 hours after unprotected intercourse as defined by lack of contraceptive use, or condom breakage or other barrier contraceptive method failure, were included. Subjects were excluded from the study in case of ongoing pregnancy or breast-feeding or current use of hormonal contraception or IUD.

Treatments

Eligible subjects received a single dose of 30 mg ulipristal acetate. Treatment was administered orally immediately after all eligibility criteria (including current pregnancy status) had been verified.

Objectives

The primary objective was to demonstrate that the pregnancy rate after taking 30 mg ulipristal acetate was statistically significantly lower than the estimated expected pregnancy rate in the study population in the absence of emergency contraception.

Secondary objectives were:

- to demonstrate that the pregnancy rate observed after taking 30 mg ulipristal acetate was statistically significantly lower than 4% (The expected pregnancy rate in the absence of back-up contraception method was estimated to be 8% according to conception probabilities provided by Trussell *et al.* (1998), and previous international studies on emergency contraception (von Hertzen *et al* 2002). A reduction of pregnancy rate by more than half of this to a pregnancy rate of 4% was considered as clinically meaningful for an emergency contraception method);
- to analyze the trend in pregnancy rate over time from the time of unprotected intercourse and to estimate the contraceptive effectiveness (prevented fraction) of 30 mg ulipristal acetate
- to study safety, tolerability and impact of ulipristal acetate on menstrual cycle length .

Endpoints

- Primary efficacy parameter:

The pregnancy rate, calculated as the number of pregnancies after emergency contraception divided by the total number of women exposed to emergency contraception for whom pregnancy status was known.

- Secondary efficacy parameter:

Contraceptive effectiveness or prevented fraction, defined as the number of pregnancies observed divided by the number of expected pregnancies based on conception probabilities (Trussell et al 1998) by cycle day of unprotected intercourse.

Subjects kept a home diary calendar from the time of treatment until study completion in which they were asked to record further intercourse during the cycle, vaginal bleeding, concomitant medications and occurrence of adverse events.

Sample size

Among the 1,623 subjects who provided informed consent and enrolled into the study, 1,533 were treated and included in the ITT population. The ITT population (N=1,533) had a mean age of 24.4 years.

Of those, a total of 1,241 subjects were eligible for the modified Intent-To-Treat population (mITT) population on which the primary efficacy analysis was performed.

Randomisation
The study was a single-arm study.

Blinding (masking)
The study was of open design and this is acceptable for the following reasons:

a) There is no comparator available with proven efficacy beyond 72 hours.
b) Placebo treatment in this indication cannot be considered ethical.
c) The outcome – pregnancy or no pregnancy – is an objective parameter which is not affected by lack of blinding.

Statistical methods
This study was specifically designed to evaluate efficacy in the time frame 48-120 hours, and included women above 18 years of age who requested emergency contraception between 48-120 hours after UPI. From international published studies it is known that the number of women requesting emergency contraception at 4-5 days after UPI is much lower than on 1-2 days, and exclusion of the time frame 1-2 days after UPI will lead to more women in the group 4-5 days after UPI. A total sample size was calculated for the whole time frame and not per day, but a separate analysis per day is provided.

The primary efficacy analysis was performed on the modified ITT population. The mITT population included women that received study drug and had at least one UPI reported at screening, and from whom pregnancy status was known. Only the first participation of the repeat enrollers (66 twice, 9 three times) was included in this modified population. Women above 35 years of age were excluded (demographics 6.7%, 90 subjects), as were 3 women with a pregnancy status that was "not compatible" (three pregnancies) with treatment failure (one subject was pregnant before treatment intake and 2 became pregnant due to intercourse that took place after emergency contraception intake).

The observed pregnancy rate was to be concluded as statistically significantly lower than the calculated expected pregnancy rate if the upper bound of the 2-sided 95% confidence interval (CI) of the observed pregnancy rate was below the calculated expected pregnancy rate. The 95% CI of the observed pregnancy rate was estimated using the Agresti-Coull interval estimation for a binomial parameter. The expected pregnancy rate was calculated as follows:

The cycle day of intercourse (cycle day relative to day of ovulation) was determined by the following formula for each subject:

> *Cycle day of intercourse = (Date of unprotected intercourse – Date of first day of last menstrual period + 1) – (Average length of menstrual cycle – 14).*

The estimated expected pregnancy rate was calculated using a pooled recognizable set of conception probabilities by cycle day relative to day of ovulation according to Trussell et al, 1998.

The interim and final analyses were performed using the Lan DeMets' alpha spending function approach, O'Brien-Flemming spending function and an information fraction of 900/1200 = 0.75. The critical value for the interim analysis was set to $z0.025 = 2.3397$ which corresponds to a probability level of 0.0193 and for the final analysis $z0.025 = 2.0117$ (instead of 1.96) which corresponds to a nominal alpha of 0.02213 and a cumulated exit probability of 0.05. Therefore 95% confidence intervals presented for primary efficacy analyses were adjusted for interim and final analyses.

The primary efficacy parameter was also analyzed for the mITT2, PP, ITT completer, ITT and repeat enrolments.

The following analyses were performed on all analysis populations:

The upper limit of the 2-sided 95% confidence interval of the observed pregnancy rate (as calculated for the primary efficacy analysis) was compared to a clinical irrelevance threshold (4%).

Probabilities of becoming pregnant according to the actual time from UPI were calculated from the logistic regression model and were graphically displayed using the spline cubic estimation (Stone & Koo, 1985).

Pregnancy rates were calculated for each of the three 24-hour intervals as well as each of the six 12-hour intervals between UPI and study medication intake and a logistic regression was used to estimate the odds ratio at a given time compared with treatment 24 or 12 hours earlier (Piaggio 1999).

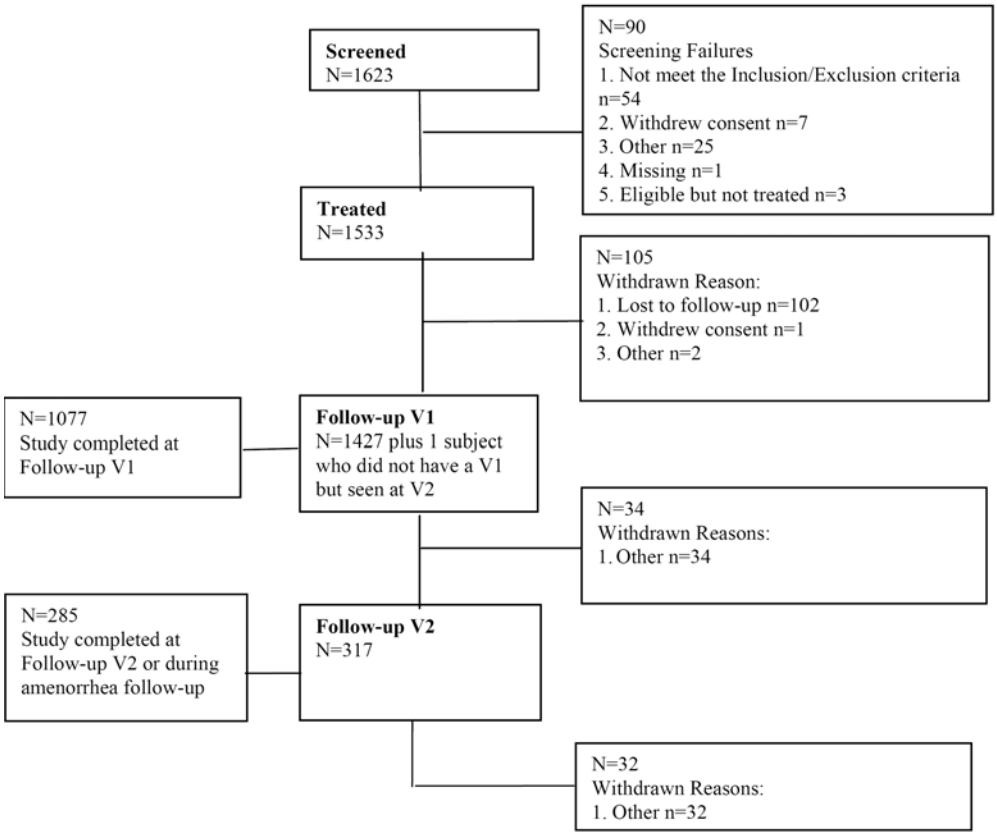
Prevented fraction was estimated with 95% CI. The 95% CI of the prevented fraction was estimated based on a method proposed by Trussell et al (1998). The prevented fraction was defined as the number of prevented pregnancies divided by the number of expected pregnancies.

Chi-square test (2-sided) was used to compare observed to expected pregnancies per cycle day.

RESULTS

Participant flow

One thousand six hundred twenty three (1,623) subjects were enrolled. Of these, 1,533 were treated including 1,507 eligible women and 26 who were treated but not eligible. Of the ITT population 848 women were administered 30 mg ulipristal acetate 48 to 72 hours after UPI, 476 women 73 to 96 hours after UPI and 200 women 97 to 120 hours after UPI. Among the treated subjects, 1,362 completed all scheduled study visits as indicated in the protocol. There were no subjects who discontinued the study due to an adverse effect. Of the treated subjects, 171 (11%) withdrew from the study, of which 102 were lost to follow-up. This percentage is comparable with the 10% anticipated for by the applicant.



Recruitment

The study started on 27 November 2006, and ended on 31 March 2008. The study was conducted at 40 study sites in different states in the US, among these were CA, MD, MI, MN, TX, UT and WA.
Subjects who presented for emergency contraception at a participating study site 48-120 hours after unprotected intercourse (UPI) and met the inclusion/exclusion criteria were enrolled into the study after they signed the informed consent form.

Conduct of the study

This was an open label single arm study. As the study was focused on a late intake (48h-120h after intercourse) and as no hormonal emergency contraception reference treatment exists for use more than 72 hours after UPI, a non-comparative design was chosen.

There were three global protocol amendments.

Baseline data

The mean age of the 1,533 subjects entered in the ITT population was 24.4 ± 6.1 years. Most women fell into the age categories 18-20 years (29.1%) and 21-25 years (39.9%). The demographics were similar to the women included in phase II studies HRA2914-507 and HRA2914-508. Besides Caucasians (60%), also a minimum proportion of 'black or African American' women were included (20%).

The average menstrual cycle length reported at inclusion was 29.0 days (range 24 - 35 days). The majority of subjects (96.0%) had regular periods in the previous year with an average of 4.7 bleeding days.

Male condom was the primary contraceptive method declared (71.7%) in the past three months at inclusion; 52.5% of subjects had used emergency contraception prior to study entry.

Of the 1,533 subjects included in the ITT population, prior to inclusion 1,301 (84.9%) of them had one unprotected intercourse, 172 (11.2%), 36 (2.3%) and 13 (0.8%) of them had 2, 3 and 4 unprotected intercourses, respectively. Two subjects (0.2%) had 5 or greater than 5 unprotected intercourses and nine (0.6%) did not have any unprotected intercourse before treatment.

Subjects enrolled reported the dates of all acts of unprotected intercourse at enrolment, with 1055 (69.2%) reporting intercourse 48 to 72 hours, 501 (32.9%) 73 to 96 hours and 199 (13.1%) more than 96 hours before study medication.

Selected baseline characteristics of subjects in Study HRA2914-509 (ITT population)

Mean Age (range)	24.4 (18.0 – 50.0)
All ages N	1533
18-20	445
21-25	611
26-30	258
31-35	119
36+	99
Ethnicity	
Hispanic	338
Non-hispanic	1182
Mean BMI (range)	25.3 (16.1 – 61.3)
Average menstrual cycle length (range)	29.0 (24.0 – 35.0)
History of amenorrhea/oligomenorrhea	7.1%
Ever pregnant yes	52.4%
Ever live birth yes	33.6%
Previous EC yes	52.5%

Time since UPI, number of subjects in each time interval (ITT population N=1524)

Time window of UPI (hours)	**N (%)**
Less than 48	136 (8.9)
48 – 60	401 (26.3)
61 – 72	518 (34.0)
73 – 84	238 (15.6)
85 – 96	263 (17.3)

Time window of UPI (hours)	N (%)
97 – 108	114 (7.5)
109 - 120	85 (5.6)

There is no indication that the study population was other than a mix of fertile women, representative as a target group for emergency contraception. The number of subjects coming at different times since unprotected intercourse appears evenly distributed across the period of interest for the study, possibly with fewer patients during the last 24h.

Numbers analysed

The primary efficacy evaluation was performed in 1241 women in the the modified ITT population (mITT). The CHMP considered acceptable to exclude repeat enrolments from mITT and they were analysed separately. It also seemed reasonable to exclude those 106 women who did not return for follow-up. The outcome of treatment in that group is not known and could theoretically include several treatment failures. The most probable fate of those subjects is, however, that they did not become pregnant. It is acceptable to exclude subjects >35 from mITT, which is likely to slightly decrease the risk of including subjects with low fertility.

Outcomes and estimation

Primary efficacy results The observed pregnancy rate (26 pregnancies) for the mITT population (N=1,241) was 2.10% (95% CI; 1.41%, 3.10%). This observed pregnancy rate was statistically significantly lower than the calculated expected pregnancy rate of 5.53%. For the ITT Completers population (29 pregnancies) comparable results were obtained: pregnancy rate of 2.17% (95% CI; 1.49%, 3.15%) and calculated expected pregnancy rate of 5.64%. Sixteen of the 29 pregnancies reported occurred outside of the defined mid-cycle "fertile period". The results obtained from the primary efficacy analysis were confirmed by the secondary efficacy measure 'supportive analysis', in which the observed pregnancies were compared to the expected pregnancies per cycle day ($p<0.001$, Chi-square test).

The pregnancy rate of 30 mg ulipristal acetate appears to be higher when indirectly compared to the published pregnancy rates within 0-72 hours of UPI of levonorgestrel, although the 95% CIs overlap, but is comparable when levonorgestrel is used after 72 hours of UPI. For levonorgestrel, pregnancy rates in published studies vary between 0.69%-1.97% when taken within 72 hours of UPI. After 72 hours (subgroup-analyses only), levonorgestrel is reported to have a drop in efficacy, and pregnancy rates of 2.44%-2.67% are observed 73-120 hours after UPI.

Secondary efficacy measures The principal secondary measure was a reduction of the *hypothesized* expected pregnancy rate of 8% with at least 50% ('clinical irrelevance threshold of 4%'), which was based on published international studies on emergency contraception. For both the mITT and the ITT Completers populations, the upper bound limit of the 95% CI of the pregnancy rate did not exceed this 4%-threshold.

The 'prevented fractions of pregnancies' for the mITT population and the ITT completers population were 62.35% (95% CI; 41.89-75.56) and 61.33% (95% CI; 41.42-74.48), respectively. These prevented fractions are comparable with prevented fractions that were reported for levonorgestrel in the time frame 73-120 hours after UPI, 60% for 2 x 0.75 mg levonorgestrel and 63% for 1.5 mg levonorgestrel (also calculated by Trussell et al.), but lower than is commonly reported for levonorgestrel within 72 hours after UPI (approximately 80%).

As another secondary efficacy measure, the 'trend in pregnancy rates' was evaluated in three 24-hour intervals. Opposed to what would be expected on the basis of data from levonorgestrel, the pregnancy rates decreased from 2.46% on day 3, to 1.91% on day 4 and 1.68% on day 5 for the ITT Completers population. Accordingly, the pregnancy rates for the mITT population were: 2.30% on day 3, 2.04% on day 4 and 1.26% on day 5.

Ancillary analyses

No subgroup examinations were planned in the protocol.

Exploratory analyses were performed of the observed pregnancy rate in the mITT population with regard to investigator, age, time from intercourse to treatment, glucocorticoids use and further UPI post treatment intake.

The only factor which exhibited any effect on the pregnancy rate was further UPI post treatment. However, due to the very small number of pregnancies, even one event would dominate the outcome.

- Analysis performed across trials (pooled analyses and meta-analyses)

Not applicable.

- Clinical studies in special populations

No studies were performed in special populations.

- Discussion on clinical efficacy

The pivotal phase III study was chosen to specifically provide data on efficacy for the interval of 48-120 hours after UPI favouring the inclusion of more women in the time frame 4-5 days after UPI. The results of this study indicated a significant over-all contraceptive effect.

Methodology

In the absence of a control group, the observed pregnancy rate was compared to the estimated pregnancy rate without use of emergency contraception, calculated by the method of Trussell et al. (Contraception 1998; 57: 363-9). It attributes a different probability of pregnancy to each day of the cycle. Subsequently, the number of expected pregnancies from a population can be obtained by multiplying the probability assigned to each day by the number of women exposed and summing up all the values corresponding to "risk days". It is noted that 16 of 29 pregnancies observed in the phase III trial occurred on days of the menstrual cycle for which the conception probability according to Trussell et al. was 0. There are published data indicating that intercourse outside of the supposed mid-cycle 'fertile period' may result in pregnancy. According to guidelines, during the average woman's menstrual cycle there are six days when intercourse can result in pregnancy, which "fertile window" comprises the five days before ovulation and the day of ovulation itself. The problem is that the day of ovulation is not known for women in clinical trials of ECs, so it has been estimated as usual cycle length minus 14 days. Only women with regular cycles can be used to estimate the expected number of pregnancies, and hence effectiveness, because otherwise the expected day of ovulation cannot be estimated. However, this estimate of the cycle day of ovulation is known to be quite imprecise and leads to the paradoxical result that many women are observed to become pregnant from intercourse occurring on cycle days with presumed zero probabilities of pregnancy.[6]

According to a prospective cohort study by Wilcox at al. (Br Med J 2001; 322:617)[7], the timing of the fertile window is highly variable, even among women who regard their menstrual cycles as regular. In this study, ovulation occurred as early as the eighth day and as late as the 60th day of the menstrual cycle. More than 70% of women are in their fertile window before day 10 or after day 17 of their menstrual cycle. There are few days of the menstrual cycle during which some women are not potentially fertile.

[6] Trussell et al. Estimating the effectiveness of emergency contraceptive pills. Contraception 2003;67:259–265
[7] Wilcox AJ, Dunson D, Baird DD. The timing of the "fertile window" in the menstrual cycle: day specific estimates from a prospective study. BMJ, 2001 Mar 10;322(7286):617

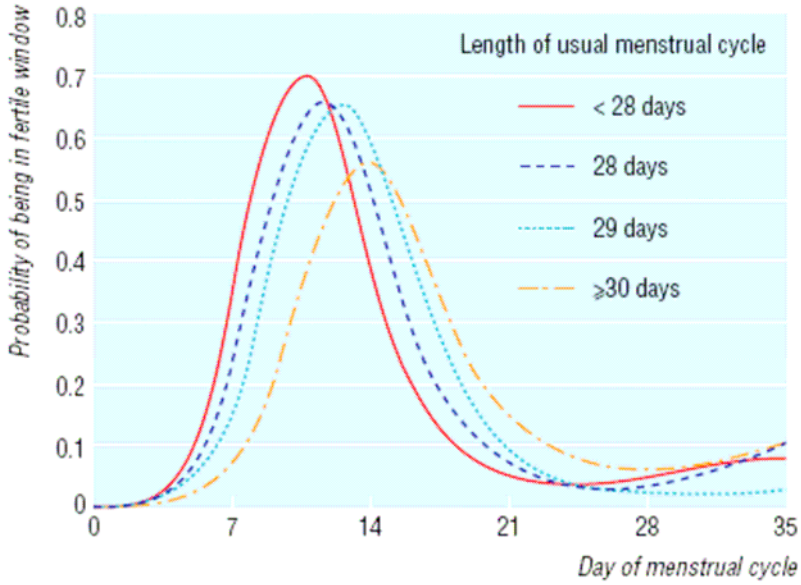


Fig 3 Probability of women with regular cycles being in fertile window, stratified by usual cycle length

Estimates of conception probabilities by cycle day of intercourse have recently been published[8], where cycle day is measured in the usual way with day 1 being the first day of bleeding in a cycle. These show that the typical woman faces a risk of pregnancy on every day of her cycle except for the first two. It was concluded that there are robust data indicating that intercourse outside of the supposed mid-cycle 'fertile period' according to Trussell (1998) may result in pregnancy. It was noted that this occurred also in the comparative phase II study, i.e. 5 pregnancies fell outside the fertile period in the levonorgestrel-treated group.

Considering the impact of these considerations on the outcome of the phase III study, the following can be concluded:

Cycle day of unprotected intercourse	Conception probability (according to Trussell et al. 1998)	N	Expected pregnancies by Trussell et al. N	Observed pregnancies N
<-5 days	**0**	**256**	**0.0**	**7**
-5 days	**3.6**	**58**	**2.1**	**0**
-4 days	**13.6**	**59**	**8.0**	**2**
-3 days	**15.5**	**70**	**10.9**	**1**
-2 days	**27.7**	**74**	**20.5**	**1**
-1 day	**29.8**	**76**	**22.6**	**3**
0 (ovulation)	**12.3**	**69**	**8.5**	**2**
+1 day	**4.5**	**59**	**2.7**	**4**
>1 day	**0**	**613**	**0.0**	**9**
		1,334	**75.3 / 1,334 = 5.64%**	**29 / 1,334 = 2.17%**

Almost two thirds of women (817/1241) were enrolled for intercourse that took place outside the presumed fertile window: of these, 16 became pregnant. As such high proportion of women were outside the supposed fertile window and were assigned a conception probability equal to zero whereas certain were in fact at risk of becoming pregnant, the CHMP agreed with the applicant that the estimated expected pregnancy rate may well be underestimated. However, on the other hand it needs

[8] Wilcox AJ, Dunson D, Baird DD. The timing of the "fertile window" in the menstrual cycle: day specific estimates from a prospective study. BMJ, 2001 Mar 10;322(7286):617

to be taken into account that new probability scores have lower probability scores on -4 days before ovulation up to day 0 (ovulation) than currently applied with conception probability by Trussell 1998. Nevertheless, all 1334 women took medication because of unprotected intercourse. Overall, there were 29 pregnancies (2.2%) observed. The expected pregnancy rate over the whole period based on Trussell's distribution would have been 75 pregnancies (5.6%). So even when bias is introduced, i.e. the extraordinary pregnancies ($7 \geq 5$ days before ovulation and $9 > 1$ day after ovulation), these figures i.e.29 pregnancies (2.17%) are still much lower than 75 pregnancies (5.64%). It is therefore concluded that adequate efficacy is shown.

Furthermore, the rate of women over-stating their risk of conception cannot be estimated. In the "worst case scenario", in a significant number of cases women might wrongly recollect the dates of the menstrual cycle if faced with the uncertainty of not obtaining emergency contraception. Sensitivity analyses were conducted to investigate the influence of possible errors in women's reporting of risk (e.g. changes in cycle dates) by moving presumed ovulation dates up to 7 days either way relative to self-estimated reporting. Those results showed that the expected pregnancy rate was only marginally affected, confirming a significant difference between expected and observed pregnancy rates. Moreover, as the date of ovulation in real life is poorly known, efficacy data were calculated assuming that all patients were completely evenly distributed across the whole menstrual cycle (instead of relying on their self-reported data). Even then, the resulting expected pregnancy rate was above the upper bound of the 95% confidence interval of the observed pregnancy rate, confirming efficacy.

The reduction of the *hypothesized* expected pregnancy rate of 8% with 50% ('clinical irrelevance threshold of 4%') is considered less relevant, as the *calculated* expected pregnancy rate was 5.64% instead of the hypothesized 8%. In this case an observed pregnancy rate of 4%, would only be a reduction in pregnancies of 29%. However, lower pregnancy rates have also been reported for other trials: the first WHO EC trial published in 1998 reported a 7.5% expected pregnancy rate according to Wilcox, corresponding to an estimated 6% expected pregnancy rate according to Trussell, and a recent review of pregnancy risk in a series of EC trials reported an expected pregnancy rate according to Trussell of 5.4%. It appears, therefore, that the expected pregnancy rate in populations seeking emergency contraception may vary from 5.4% to 8%.

The primary efficacy analysis was performed in the mITT population. This is not considered appropriate, as the exclusion of women above 35 years of age is not supported, nor the exclusion of the subjects with pregnancies determined as "not compatible". The conception probabilities by Trussell et al. used to calculate the expected pregnancy rate were based on studies which also included women above 35 years of age. Moreover, exclusion of >35 years was not present in **HRA2914-507, HRA2814-508** and in other published studies. The ITT Completers Population, which includes women above >35 years and pregnancies considered "not compatible", is therefore seen as the most important population, and the primary focus in this assessment. However, in this case the CHMP did not consider this an issue, because the results of the mITT population and the ITT Completers population are comparable.

Results

As another secondary efficacy measure, a separate analysis was made for days 3, 4 and 5. This is an important point, because up till now emergency contraception with levonorgestrel has been restricted up to 72 hours. As expected, more women were included on day 3 after UPI (n= 735), than on day 4 (n = 420) and 5 after UPI (n=179), which makes the efficacy assessment during the period 96-120 h difficult. The observed pregnancy rate, the number of expected pregnancies and the prevented fraction with accompanying 95% confidence intervals, during the different time intervals (48-72h; 72-96h; 96-120h) has been calculated.

The results of the submitted subgroups analyses is presented in the next table:

Time window	mITT (n)	Obs. Pregnancies (n)	Exp. Pregnancies (n)	Obs. Pregnancy Rate [95% CI]	Exp. Pregnancy Rate	Prevented Fraction [95% CI]	RR^A [95% CI])
[48h-72h]	693 (56%)	16	42	2.31 % [1.4%-3.75%]	6.01%	61.9% [36.3%-77.2%]	2.62 [1.57 ; 4.39]
[72h-96h]	390 (31%)	8	19	2.05% [0.97%-4.07%]	4.95%	57.9% [14.6%-79.2%]	2.38 [1.17 ; 4.81]
[96h-120h]	158 (13%)	2	8	1.27% [0.05%-4.79%]	4.90%	75.0 % [6.2%-93.3%]	4.00 [1.07; 14.9]

RR^A Relative risk by assessor based on RR=1/(1-PF)

The number of women included in each subgroup analysis is low which increases the degree of uncertainty of the point estimates, as can be observed by the widening of the 95% CI's. However, the results are consistent with the overall analysis for the following reasons:

The observed pregnancy rates in the 3 subgroups are within the range of that noted for the overall pregnancy rate, i.e. noted for the total time frame of 48-120 hours [2.10 (1.41 – 3.10)], as are the prevented fractions (48-120 hours: 62.3%). The 95% confidence intervals are rather broad which is not unexpected as the numbers in the subgroups decreases drastically. As a result, the degree of uncertainty is increased. However, the confidence interval over the observed pregnancy rate does not allow a useful interpretation as it is the difference between expected and observed pregnancy rate and its uncertainty which is of interest.

The prevented fraction takes this difference into account and is thus more useful. Several conclusions can be drawn:

- Although the 95% confidence intervals are wide, the confidence intervals of the prevented fraction do not include 0%, indicating that there is pregnancy protection.
- Moreover, the point estimate is considered the best estimate, and it is extremely unlikely that, if the study would be repeated, these point estimates would diverge drastically from the currently calculated point estimates.
- The point estimates for the subgroups are consistent.
- The prevented fraction can also be converted in the relative risk of pregnancy between non-users versus Ellaone users, which may give more clarity. The risk of pregnancy in non-users is 2.6, 2.4, and 4 times larger, respectively, at day 3, 4, and 5 as compared to Ellaone users. Again, confidence intervals are wide but do not include 1 (1 would indicate no difference) and are consistent for all three comparisons.

In conclusion, although the study was not powered to demonstrate efficacy per 24 hour time frame, these subgroup analyses can be considered supportive of efficacy across the whole time frame of 48-120 hours after UPI.

An overall pregnancy rate of 2.17% for the ITT Completers population in the time frame 48-120 hours was considered acceptable, as well as the prevented fraction of 61%.

As an additional analysis was performed in the ITT completer population (n = 1302 women) with no additional use of emergency contraception during treatment cycle (population called "ITT completer 2"). The efficacy results presented in the following table provide 95% CI for both observed pregnancy rate and expected pregnancy rate (Trussell) on and mITT populations.

Table: Observed and expected pregnancy rate on mITT completer 2 and on mITT populations

Population	Nb Treated	Nb Observed Pregnancies	Observed Pregnancy Rate [95% CI]	Expected Pregnancy Rate [95% CI]
ITT completer 2*	1302	28	2.15% [1.46% - 3.13%]	5.64% [4.56% - 6.72%]
mITT	1241	26	2.10% [1.41% - 3.10%]	5.53% [4.47% - 6.60%]

* "ITT completer 2" population corresponds to "ITT completers" population who did not use any additional emergency contraception during the trial

These additional analyses indicated that the possible inclusion in the analysis of those women who did use emergency contraception more than once during the treatment cycle did not relevantly change the observed and expected pregnancy rates.

The applicant did not investigate the effect of multiple acts of intercourse or contraceptive failures on the pregnancy rate. Even more, most of the women had had only one act of unprotected intercourse, 84.4% in the ITT Completers population. Therefore, the claim "*one or more acts of*" was removed from the indication, as this had not been specifically studied.

Another issue is the use in adolescents younger than 18 years of age. The applicant has submitted a paediatric investigation plan on 24 July 2008 to the EMEA (EMEA-000305-PIP-01) in which they propose to perform the following clinical studies:

- Single-blind, multicentre, randomized, parallel group safety and efficacy study of ulipristal acetate 30 mg versus levonorgestrel 1.5 mg for emergency contraception within 120 hours of unprotected intercourse, in adolescents (and in adults).
- Open-label, observational safety study of ulipristal acetate for emergency contraception within 120 hours of unprotected intercourse, in adolescents (and in adults).

Finally, a major restriction of the pivotal clinical study was that it did not provide data for the time frame of 0-48 hours after UPI. This had been studied in the pivotal phase II studies HRA2914-507 and HRA2914-508 that were carried out with the 50 mg unmicronized formulation. A clinical effect was shown in both studies with non-inferiority of 50 mg unmicronized ulipristal acetate to levonorgestrel twice 0.75 mg within 72 hours after UPI, but the adequacy of pharmacokinetic data provided to bridge the 50 mg unmicronized and 30 mg micronized dosages was questioned.

For this reason, the Applicant provided during the course of the procedure the interim analysis of efficacy results obtained in the ongoing comparative Phase III clinical study (HRA2914-513).

- **Ongoing comparative Phase III clinical study (HRA2914-513) (interim analysis results)**

The protocol of trial HRA2914-513 had not been included in the original dossier by the applicant. The results of an interim analysis and the protocol were received during the assessment procedure.

Study HRA2914-503 concerns a prospective, randomized, single blind, multicenter study to compare the efficacy, safety and tolerability of ulipristal acetate with levonorgestrel as emergency contraception within 120 hours of unprotected intercourse. The treatments were administered in a single-blind fashion, with the treatment identity known by the study staff but unknown by the subjects and the sponsor.

The primary objective was to demonstrate that the pregnancy rate observed after taking ulipristal acetate (30 mg tablet micronized) within 72 hours of UPI is statistically significantly lower than the estimated expected pregnancy rate in the absence of emergency contraception.
There were nine secondary objectives, from which the following objectives are considered the most important:

- To demonstrate that the pregnancy rate observed after taking ulipristal acetate (30 mg tablet micronized) within 72 hours of UPI is statistically significantly lower than 4% considered as a clinical irrelevance threshold.
- To demonstrate the non-inferiority of ulipristal acetate 30 mg versus levonorgestrel 1.5 mg as EC within 72 hours of UPI. Should non-inferiority be demonstrated, superiority will be tested.
- To demonstrate the non-inferiority of ulipristal acetate 30 mg versus levonorgestrel 1.5 mg as EC within 120 hours of UPI. Should non-inferiority be demonstrated, superiority will be tested.

Sample size calculations were based on the primary efficacy analysis, and the main secondary analysis (inferiority to clinical threshold) and the non-inferiority of ulipristal acetate 30 mg versus levonorgestrel 1.5 mg as EC within 72 hours of UPI. In order to reach at least 85% power with an equivalence margin of 1.6 in odds ratio, 1022 patients per group were randomized for a total of 2044 patients.
Because the primary efficacy analysis was based on the 0-72 h interval, study enrollment was supposed to be stopped once 827 patients meeting criteria for the primary efficacy population per group in this time interval had completed the study.

Interim analysis
In the protocol it was predefined that an interim analysis was to be performed once 1200 patients meeting criteria for primary efficacy evaluation had completed the study.
Three efficacy analyses were performed at the interim analysis: Primary efficacy analysis, inferiority to clinical irrelevance threshold and non-inferiority analysis to Levonelle.
In the event that the upper limit of the confidence interval of the pregnancy rate in the mITT population was below the estimated expected pregnancy rate and below the clinical irrelevance threshold of 4%, and that ulipristal acetate was non inferior to levonorgestrel, the study would be considered positive and recruitment will be stopped. Using Lan DeMets' alpha spending function approach, O'Brien-Flemming spending function and an information fraction of 1200/1654 = 0.72, we get a critical value for the interim analysis equals to $z_{0,025}$ = 2,3876 which corresponds to a probability level of 0,01696 and for the final analysis $z_{0,025}$ = 2,0056 (instead of 1.96) which corresponds to a nominal alpha of 0,02245 and a cumulated exit probability of 0.05.
In practice, the confidence interval will be computed using a $Z_{\alpha/2}$ equal to 2,3876 at the interim analysis and equal to 2,0056 at the final analysis (instead of 1.96).
The power of the final analysis is approximately 82.4% and the power of the interim analysis is approximately 56.5%.

Since the results satisfied the statistical criteria for efficacy as defined in the protocol and the interim analysis SAP, the applicant decided to stop recruitment in the study as of 4 February 2009.

Results
As planned in the protocol, the interim analysis was performed on data from the first 1200 mITT subjects enrolled within 72 hours of unprotected intercourse (UPI).

According to the statistical analysis plan for the interim analysis, three analyses were performed:

1) Primary efficacy analysis: comparison of the upper limit of the 95% CI of the observed ulipristal acetate pregnancy rate to the expected pregnancy rate (calculated by the method of Trussell et al. 1998) in the absence of emergency contraception.
2) Inferiority to clinical irrelevance threshold: comparison of the upper limit of the 95% CI of the observed ulipristal acetate pregnancy rate to the threshold of 4%.
3) Non-inferiority analysis: comparison of the upper bound of the 95% CI of the pregnancy odds ratio in the ulipristal acetate group relative to that in the levonorgestrel group versus the non-inferiority margin of 1.6.

- Estimation of the odds ratio is adjusted for expected pregnancy rate through a logistic model.
- ***Confidence intervals are adjusted for the interim analysis*** – the used critical value is 2.3786 instead of 1.96. Confidence intervals of non adjusted results are not presented but are narrower.

The 1200 mITT subjects included in the analysis were distributed as follows among the three 24-h intervals between UPI and treatment:

- [0-24h]: 458 (38.2%);
- [24-48h]:452 (37.7%);
- [48-72h]: 290 (24.2%).

The observed pregnancy rate with ulipristal acetate over the 0-72h time interval was 1.51% [0.62% - 3.32%], and the results of the three analysis satisfied the statistical criteria for efficacy as defined in the protocol and the interim analysis SAP.

Blinded results were provided over the whole 120h interval. Based on the ongoing database as of January 27, 2009, 2048 subjects had been enrolled overall. Among them, 214 (10.4%) presented in [72-120h] time window and 3 subjects were pregnant at follow-up. No calculations were presented on pregnancy rates based on these data, because a number of subjects were still undergoing follow-up.

Because the results of the interim analysis satisfied the statistical criteria for efficacy as defined in the protocol, the applicant decided to stop recruitment in the study as of 4 February 2009. Clinical investigators, study staff and other involved parties had been informed of this decision, but specific results had not been disclosed. Investigators were instructed to perform follow up of all enrolled subjects to completion as per the study protocol, and the Applicant intended to proceed with cleaning the full database in a blinded fashion before code break. The full study report of **HRA2915-513** will be available by the end of July 2009.

In conclusion, the results from the interim analysis support adequate efficacy for the time interval 0-72 hours. Furthermore, despite the fact that the interim analysis did not provide efficacy data for the time interval 73 – 120 hours for ulipristal acetate, the 4 pregnancies reported among 232 women (from the whole study population of 2048 subjects) who had been randomized to ulipristal acetate or levonorgestrel, suggested a low pregnancy rate also in that time interval.

Clinical safety

The safety data presented summarized adverse events for all subjects who were included in the 6 phase I studies, 2 phase II studies and 1 phase III study. Also, serious adverse events of an ongoing phase III trial were incorporated. Overall, the safety profile reported for ulipristal acetate was comparable to that reported for levonorgestrel, registered for emergency contraception up to 72 hours after UPI. The most frequently observed adverse events in the phase III trial were headache, nausea and abdominal pain.

- Patient exposure

Overall, 3,560 subjects were evaluated for safety of ulipristal acetate. The number of patients exposed in the phase II and III studies was 3,391, from which 1,533 subjects received the dose to-be-marketed.
In the phase II studies, four multiple enrolments occurred. Seventy-five women were enrolled on multiple occasions in the phase III study (66 twice and 9 three times). Multiple enrollers were defined as subjects who were enrolled and treated more than once.
In the 3 completed safety & efficacy studies performed in the USA (**HRA2914-507**, **HRA2914-508** and **HRA2914-509**), 214 subjects received 10 mg unmicronized ulipristal acetate, 399 received 10 mg micronized ulipristal acetate, 1533 received 30 mg micronized ulipristal acetate, 1,245 received 50 mg unmicronized ulipristal acetate and 840 received 2 x 0.75 mg levonorgestrel. Safety data is considered adequate for exposure to 30 mg micronized ulipristal acetate single-dose administration. No long-term safety data is required for the 30 mg formulation, as the indication emergency contraception concerns only a single dose. The subjects were in general healthy women with a mean age of 24 years. No

significant differences were observed between the treatment groups for age, race, height, and body weight in the phase II studies. The baseline characteristics of the phase III trial were comparable with the characteristics of the subjects included in the phase II trials. The majority of the women were white (60.3%), but a reasonable percentage belonged to other racial groups, for instance Black or African American (21.5%).

- Adverse events

AEs were generally similar in both treatment groups in the two phase II studies, with 73% of subjects who experienced one or more AEs in the 10 mg unmicronized group, 79% in the 10 mg micronized group, 77% in the 50 mg unmicronized group and 76% in the levonorgestrel group. The incidence of AEs is higher than was previously reported for levonorgestrel 2x0.75 mg 12 hours apart. The higher incidence is not a reason for concern, as this could well be a consequence of the three-day diary with a yes/no response to a predefined checklist. Ovarian pain was higher in the ulipristal acetate groups (7% unmicronized 10 mg, 6% micronized 10 mg, 3% unmicronized 50 mg) compared to levonorgestrel (1%). 'Ovarian pain', though suggesting an etiologic cause, however appeared to have low significance from a medical standpoint. Further information on the possible relationship of ovarian pain and the presence of ovarian cysts indicated that in the clinical studies 'ovarian pain' was mainly mild or moderate in intensity, not dose-dependent and not suggestive of ovarian cyst-related pain. Incidence of severe or moderate ovarian pain was reported in only 2 women and treatment was only necessary in 3 women. It is therefore concluded that there is insufficient evidence to directly relate this symptom to the possible presence of functional cysts. However, the use of this term will nevertheless cause confusion regarding its etiology.

During the phase III trial, 876 (61.4%) subjects experienced at least one AE. The majority (89.1%) of the AEs were mild or moderate in intensity. The most common AEs were headache (17.5%), nausea (12.2%) and abdominal pain (11.7%). The frequencies are comparable for what has been reported for levonorgestrel. The AEs are well reflected in section 4.8 of the proposed SPC. Vomiting was observed in 2% of the subjects, therefore what to do in case of vomiting after intake of the 30 mg tablet has been included in section 4.2 of the SPC.

The **post-treatment cycle length** was 2.9 days longer from average length in the phase III trial. A shortened menstrual cycle was reported in some women: in study HRA2914-509, 96 (6.1%) women in the ITT population reported onset of menses earlier than expected by 1 week or more. 14 women (0.9%) reported onset of menses earlier than expected by 2 weeks or more. 19.2% had a change in cycle length greater than 7 days, and 5.1% greater than 20 days. Seven out of 1,336 subjects had still not experienced menstrual bleeding 60 days after expected menses. From the 3 subjects that underwent clinical investigations, the menses returned after approximately 100 days. In one case, amenorrhea might be explained by polycystic ovary syndrome (PCOS). One subject had full amenorrhea exams performed with unknown diagnosis and menses returned 4 months after expected onset of menses. Unfortunately, 3 of the 4 women in whom ongoing amenorrhoea was noted were lost to follow-up. However, incidence of amenorrhoea is taken into account in the RMP.
The delay in menstrual bleeding is mentioned in section 4.4. of the SPC. An increase of 7-20 days in the post-treatment cycle is considered acceptable. Although it is expected that subsequent menstrual cycles will return to their pretreatment pattern, no information is present in the file.

A dose-response relationship was observed in the pharmacodynamic studies between ulipristal acetate and the presence of **ovarian cysts**. There were three women with cysts which did not resolve spontaneously, leading to one case of surgery for a ruptured cysts and a 90-day cycle, and one ovariectomy. Unfortunately, no ultrasound was performed in the pivotal phase III-trial. Based on pharmacodynamic studies that evaluated women by ultrasound there is no clear dose-response relation with regard to the incidence of cysts, but the number of women evaluated is low and it is therefore agreed with the applicant that a dose-response relation or a causal relation with ulipristal acetate cannot be excluded. It is considered reassuring that the pivotal phase II study and phase III study did not report symptomatic ovarian cysts. Nevertheless, occurrence of ovarian cysts is also reported with hormonal contraception and other medicinal products that interfere with the pituitary-ovarian axis. It is therefore recommended to include occurrence of ovarian cysts in the RMP.

No case of endometrial hyperplasia was noted in the **endometrial biopsies** taken after 12-weeks administration of micronized ulipristal acetate up to 10 mg/day. However, after single-dose administration endometrial hyperplasia was noted in 1 out of 55 subjects in the **HRA2914-506** study, but at follow-up two months after treatment only stromal glandular desynchrony was observed. It is considered very unlikely that a single-dose administration would be capable to induce adverse endometrial effects.

Data regarding **pregnancy** was very limited. Of the 29 treated subjects in the Phase III trial who became pregnant, 16 elected to have an induced abortion, 6 reported spontaneous abortion, 6 decided to carry the pregnancy to term, and 1 was lost to follow-up. At the time of database lock, 5 of the 6 pregnancies to be carried to term were still ongoing; one woman expected to deliver in December 2007 refused to release information on the birth status.

Table 13: Pregnancies and outcome in ulipristal acetate studies

Study	Nb of pregnancies in ulipristal acetate group (Nb considered as not being a treatment failure)	Pregnancy Outcome
HRA2914-503 (95-CH-168) (Placebo, 1, 10, 50 10, 200 mg ulipristal acetate) NB: PK study	200 mg: 1 (NA)	**200 mg unmicronized:** - 1 normal live birth
HRA2914-507 (CCN-002) (50 mg non micronized ulipristal acetate versus levonorgestrel)	50 mg: 12 (4) Levo: 14 (1)	**50 mg unmicronized:** - 9 induced abortions - 1 spontaneous abortions - 2 unknown **Levonorgestrel:** - 8 induced abortions - 4 spontaneous abortion - 1 biochemical Pregnancy - 1 normal live birth
HRA2914-508 (CCN-002 ext) (50 mg non micronized, 10 mg micronized and 10 mg non micronized ulipristal acetate)	10 mg micro: 11 (1) 50 mg: 5 (0) 10 mg unmic: 13 (2)	**10 mg micronized:** - 9 induced abortions - 1 normal live birth - 1 unknown **50 mg unmicronized:** - 4 induced abortions - 1 normal live birth **10 mg unmicronized:** - 8 induced abortions - 2 spontaneous abortions - 3 unknown
HRA2914-509 (2914-005) (30 mg micronized ulipristal acetate)	29 (3)	**30 mg micronized** - 16 induced abortions - 6 spontaneous abortions - 1 normal live birth - 6 lost to follow-up (among 5 declared they wanted to continue with pregnancy)

The available data indicate 4 normal live births as a pregnancy outcome after exposure to ulipristal acetate in different doses. Five of the 6 women who decided to continue pregnancy in study 509 were lost-to-follow up. This means that there is extremely limited data regarding pregnancy outcome after exposure to ulipristal acetate, which is also stated in the SPC. More information on pregnancy

outcome is needed and is included in the RMP. The SPC includes a statement that HRA Pharma maintains a pregnancy registry to monitor outcomes of pregnancy in women exposed to Ellaone.

Discontinuations Only two subjects were withdrawn due to an AE: hyperthyroidism secondary to thyroiditis and abdominal pain and fever.

Adverse reactions (events judged at least possibly related to treatment) reported during treatment with ulipristal acetate

MedDRA	Adverse reactions (%frequency)			
System Organ Class	**Very common ≥ 1/10**	**Common ≥ 1/100 to < 1/10**	**Uncommon ≥ 1/1000 to < 1/100**	**Rare ≥ 1/10000 to < 1/1000**
Infections and infestations		Infections 1.5 **		
Metabolism and nutrition disorders			Appetite disorders 0.5	Dehydration 0.07
Psychiatric disorders		Mood disorders 1.3	Depression 0.1 Anxiety symptoms 0.4 Insomnia 0.34 Libido disorders 0.2 Irritability 0.2	
Nervous system disorders		Headache 9.8 Dizziness 3.5	Somnolence 0.8 Tremor 0.1	Disturbance in attention 0.07 Dysgueusia 0.07 Lethargy 0.07
Eye disorders			Vision blurred 0.3	
Ear and labyrinth disorders				Vertigo 0.07
Vascular disorders			Hot flush 0.4	
Respiratory, thoracic and mediastinal disorders				Sinus congestion 0.07 Cough 0.07 Epistaxis 0.07 Dry throat 0.07
Gastrointestinal disorders	Abdominal pain 12.97	Nausea 9.2 Vomiting 1.0 Dyspepsia1.0	Diarrhoea 0.7 Constipation 0.3 Dry mouth 0.3 Flatulence 0.1	Gastro-oesophageal reflux disease 0.07 Glossitis 0.07 Toothache 0.07
Skin and subcutaneous tissue disorders			Acne 0.7 Rash 0.1 Pruritus 0.2	Urticaria 0.07
Musculoskeletal and connective tissue disorders		Muscle spasms 1.4 Back pain 1.0	Musculoskeletal pain 0.3	
Renal and urinary disorders			Pollakiuria 0.1	Nephrolithiasis 0.07 Renal Pain 0.07 Chromaturia 0.07
Reproductive system and breast disorders	Menstrual disorder 19.2	Dysmenorrhea 4.1 Menorrhagia 1.0 Metrorrhagia 8.7	Breast pain 0.7 Genital pain 0.3 Uterine spasm 0.5 Premenstrual syndrome 0.2 Genital pruritus 0.1 Vaginal discharge 0.8	Ruptured ovarian cyst 0.07
General disorders and administration site conditions		Fatigue 3.5	Pain 0.7	Chest discomfort 0.07 Inflammation 0.07 Malaise 0.07 Pyrexia 0.07 Thirst 0.07 Chills 0.07

***** Not listed as an adverse reaction in section 4.8 of proposed SPC because pregnancy outcome is addressed in section 4.6.

- Serious adverse event/deaths/other significant events

No deaths were reported in any completed or ongoing studies.
Nine serious adverse events occurred (bacterial pneumopathy, abdominal pain and fever, Grave's disease, kidney infection, pelvic inflammatory disease (PID), seizure, pelvic pain associated with urinary tract infection, stomach ulcer, vomiting blood-stained fluid). All SAEs were considered not related to the study drug, including the one case of PID.

- Laboratory findings

Laboratory results do not seem to alter significantly when pre- and post-treatment values are compared. The original Phase III study design (HRA2914-509) did not include any laboratory analyses, but following the results of a US FDA Special Protocol Assessment procedure the protocol was amended in order to obtain data on safety laboratory parameters in a sample of subjects with the final dosage form of the drug.

- Safety in special populations

Intrinsic factor: age
The frequency and profile of AEs were comparable in the ITT population and in the population aged 35 years or less (mITT population).
Given the population that is expected to use Ellaone in daily practice, the absence of information regarding effects in post pubertal children might represent a safety concern. The safety in post pubertal children will be addressed within the Paediatric Investigation Plan.

Hepatic and renally impaired populations
The applicant was requested to provide any available information on the efficacy and safety of Ellaone in hepatic and renal impaired populations in the current clinical studies. The fact that no inquiries regarding liver or renal impairment were received does not directly implicate that no safety issue exists. However, requesting specific pharmacokinetic studies would lead to unnecessary exposure in women with renal and liver impairment. Ulipristal acetate is primarily metabolised in the liver and no relevant effect on PK parameters of ulipristal acetate in women with renal impairment is expected. In women with hepatic impairment PK may be affected but it should be taken into consideration that ulipristal acetate is given only as one single tablet and it is unlikely that these women will be candidates for this kind of treatment. The current SPC text under 4.2, mentioning that use of ulipristal acetate is not recommended in females with severe hepatic impairment, is therefore considered sufficient.

- Safety related to drug-drug interactions and other interactions

No specific study or analysis of drug interactions was performed.

- Discontinuation due to adverse events

As almost all studies were performed with a single-dose administration, consequently the discontinuation due to significant adverse events is extremely low.
Only two subjects were withdrawn due to AE: one in study **HRA2914-501** (hyperthyroidism secondary to thyroiditis) and one in study **HRA2914-510** (abdominal pain and fever).

- Post marketing experience

Ulipristal acetate is not yet marketed in any dose in any country. Therefore, no post-marketing data is available.

- Discussion on clinical safety

Ulipristal acetate single-dose in general appears to be well tolerated, and has an AE profile comparable with levonorgestrel. However, several concerns remain:

- The pregnancy follow-up so far is very limited and no conclusions can be drawn with regard to safety, should the woman take ulipristal acetate in very early pregnancy. Pregnancy follow-up will be an important part of the risk management plan. In the section 4.2 it is stated that pregnancy should be excluded, if suspected, before Ellaone is administered.

- The effect of a single-dose administration on the development of ovarian cysts and amenorrhea. Current safety data suggest reversible occurrence of ovarian cysts and delay in return of menstrual bleeding. Spontaneous reports of these adverse events need to be followed up closely in the PSURs, see also RMP.

- In theory, a woman may request emergency contraception repeatedly, either in the same menstrual cycle or in subsequent cycles. In the SPC statements have been added in section 4.4 to address this issue.

2.5. Pharmacovigilance

Detailed description of the Pharmacovigilance system

The CHMP considered that the Pharmacovigilance system has deficiencies that should be addressed as part of the follow up measures.

The applicant committed that the deficiencies will be rectified prior to placing the medicinal product on the market. The procedures will be updated by June 2009.

Risk Management Plan

The MAA submitted a risk management plan, which included a risk minimisation plan

Summary of the risk management plan for Ellaone

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimisation
Identified risks:		
Abdominal pain	Routine pharmacovigilance	Mention in SPC Section 4.8
Nausea	Routine pharmacovigilance	Mention in SPC Section 4.8
Dizziness	Routine pharmacovigilance	Mention in SPC Section 4.8
Headache	Routine pharmacovigilance	Mention in SPC Section 4.8
Dysmenorrhoea	Routine pharmacovigilance	Mention in SPC Section 4.8
Potential risks:		
Increase in blood pressure	- Routine pharmacovigilance - Special attention in PSURs	

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimisation
Liver effects	- Routine pharmacovigilance - Use of specific report form for spontaneous report - Special attention in PSURs	
Effect on pregnancy maintenance / off-label use as abortifacient	- Routine pharmacovigilance - Use of specific report form for spontaneous report - Special attention in PSURs - Peri/post natal toxicity study in rat (HRA2914-453) - Follow-up of any pregnancy occurring in treated patient of the ongoing phase III study (HRA2914-513) - Observational study within the frame of the Paediatric Investigation Plan (PIP) (HRA2914-515) - Registry of exposed pregnancies - Clinical follow-up of pregnancies in the practice of 1000 targeted prescribers - Study using prescription registries to identify off-label use	Omit any sentence in the SPC and the PL suggesting that the product could be used as an abortifacient. SPC section 4.2: Pregnancy should be excluded before Ellaone is administered. SPC section 4.3: Contraindication : Pregnancy SPC Section 4.6: Ellaone is contra-indicated during an existing or suspected pregnancy (see section 4.3). Extremely limited data are available on the health of the foetus/new-born in case a pregnancy is exposed to ulipristal acetate. Although no teratogenic potential was observed, animal data are insufficient with regard to reproduction toxicity (see section 5.3). SPC section 5.1 : Ulipristal acetate is an orally-active synthetic progesterone receptor modulator which acts via high affinity binding to the human progesterone receptor.
Unintended pregnancy exposure and the risk of incomplete abortion and heavy bleeding	- Routine pharmacovigilance - Use of specific report form for spontaneous report - Special attention in PSURs - Peri/post natal toxicity study in rat (HRA2914-453) - Follow-up of any pregnancy occurring in treated patient of the ongoing phase III study (HRA2914-513) - Observational study within the frame of the Paediatric Investigation Plan (PIP) (HRA2914-515) - Registry of exposed pregnancies - Clinical follow-up of pregnancies in the practice of 1000 targeted prescribers	SPC section 4.3: Contraindication : Pregnancy SPC Section 4.4 In case of doubt, delay of more than 7 days in next menstrual period, abnormal bleeding at the expected date of menses, or symptoms of pregnancy, pregnancy should be excluded by a pregnancy test. SPC Section 4.6: Ellaone is contra-indicated during an existing or suspected pregnancy (see section 4.3). Extremely limited data are available on the health of the foetus/new-born in case a pregnancy is exposed to ulipristal acetate. Although no teratogenic potential was observed, animal data are insufficient with regard to reproduction toxicity (see section 5.3).
Unintended pregnancy exposure (risk of	- Routine pharmacovigilance - Special attention in PSURs	SPC section 4.3: Contraindication : Pregnancy

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimisation
malformations)	- Use of specific report form for spontaneous report - Peri/post natal toxicity study in rat (HRA2914-453) - Follow-up of any pregnancy occurring in treated patient of the ongoing phase III study (HRA2914-513) - Observational study within the frame of the Paediatric Investigation Plan (PIP) (HRA2914-515) - Registry of exposed pregnancies - Clinical follow-up of pregnancies in the practice of 1000 targeted prescribers	SPC Section 4.6: Ellaone is contra-indicated during an existing or suspected pregnancy (see section 4.3). Extremely limited data are available on the health of the foetus/new-born in case a pregnancy is exposed to ulipristal acetate. Although no teratogenic potential was observed, animal data are insufficient with regard to reproduction toxicity (see section 5.3).
Risk of ectopic pregnancy	- Routine pharmacovigilance - Use of specific report form for spontaneous report - Special attention in PSURs - Follow-up of any pregnancy occurring in treated patient of the ongoing phase III study (HRA2914-513) - Observational study within the frame of the Paediatric Investigation Plan (PIP) (HRA2914-515) - Registry of exposed pregnancies - Clinical follow-up of pregnancies in the practice of 1000 targeted prescribers	Section 4.4: If pregnancy occurs after treatment with Ellaone, as for all pregnancies, the possibility of an ectopic pregnancy should be considered. Ectopic pregnancy may continue despite the occurrence of uterine bleeding.
Other adverse pregnancy effects (eg perinatal/neonatal effects) depending on time of foetal exposure	- Routine pharmacovigilance - Use of specific report form - for spontaneous report - Special attention in PSURs - Peri/post natal toxicity study in rats (HRA2914-453) - Follow-up of any pregnancy occurring in treated patient of the ongoing phase III study (HRA2914-513) - Observational study within the frame of the Paediatric Investigation Plan (PIP) (HRA2914-515) - Registry of exposed	SPC section 4.3: Contraindication: Pregnancy SPC Section 4.6: Ellaone is contra-indicated during an existing or suspected pregnancy (see section 4.3). Extremely limited data are available on the health of the foetus/new-born in case a pregnancy is exposed to ulipristal acetate. Although no teratogenic potential was observed, animal data are insufficient with regard to reproduction toxicity (see section 5.3).

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimisation
	pregnancies - Clinical follow-up of pregnancies in the practice of 1000 targeted prescribers	
Effects in pregnancy in case of treatment failure	- Routine pharmacovigilance - Use of specific report form for spontaneous report - Special attention in PSURs - Peri/post natal toxicity study in rat (HRA2914-453) - Follow-up of any pregnancy occurring in treated patient of the ongoing phase III study (HRA2914-513) - Observational study within the frame of the Paediatric Investigation Plan (PIP) (HRA2914-515) - Registry of exposed pregnancies - Clinical follow-up of pregnancies in the practice of 1000 targeted prescribers	SPC Section 4.6: Ellaone is contra-indicated during an existing or suspected pregnancy (see section 4.3). Extremely limited data are available on the health of the foetus/new-born in case a pregnancy is exposed to ulipristal acetate. Although no teratogenic potential was observed, animal data are insufficient with regard to reproduction toxicity (see section 5.3).
Delayed menstrual period > 60 days / amenorrhea	- Routine pharmacovigilance - Special attention in PSURs	SPC Section 4.8: 0.5 % of women experienced a delay of more than 60 days beyond the anticipated onset of menses.
Ovarian cysts	- Routine pharmacovigilance - Special attention in PSURs	SPC Section 4.8 : Ruptured ovarian cyst
<u>Missing information:</u>		
Effect in post pubertal children	- Routine pharmacovigilance - Follow-up of any pregnancy occurring in treated patient of the ongoing phase III study (HRA2914-513) - Observational study within the frame of the Paediatric Investigation Plan (PIP) (HRA2914-515)	SPC Section 4.2: Safety and efficacy of Ellaone was only established in women 18 years and older
Effect in lactating women	- Routine pharmacovigilance - Assessment of excretion in milk in rats (HRA2914-453) - Pharmacokinetic study in lactating women if the rat study is positive (HRA2914-514)	SPC Section 4.6: It is unknown whether ulipristal acetate is excreted in human or animal breast milk. Ulipristal acetate is a lipophilic compound and may theoretically be excreted in breast milk. A risk to the breast-fed child cannot be excluded. After intake of Ellaone breastfeeding is not recommended for at least 36 hours.

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimisation
Effect of concomitant use of potent CYP3A4 inducers or inhibitors	Routine pharmacovigilance	SPC Section 4.5: CYP3A4 inducers (e.g.. rifampicin, phenytoin, phenobarbital, carbamazepine, ritonavir, St John's wort/Hypericum perforatum) may reduce plasma concentrations of ulipristal acetate and may result in decrease in efficacy. Concomitant use is therefore not recommended. Enzyme induction wears off slowly and effects on the plasma concentrations of ulipristal acetate may occur even if a woman has stopped taking an enzyme inducer within the last 2-3 weeks." Concomitant administration of potent CYP3A4 inhibitors (e.g. ketoconazole, itraconazole, telithromycin, clarithromycin, nefazodone) may increase exposure to ulipristal acetate. The clinical relevance is unknown.
Effect of concomitant use of drugs that increase gastric pH	Routine pharmacovigilance	SPC section 4.5: Concomitant administration of drugs that increase gastric pH (e.g. proton pump inhibitors, antacids and H2-receptor antagonists) may reduce plasma concentrations of ulipristal acetate and may result in decrease in efficacy. Concomitant use is therefore not recommended.
Effect of concomitant use of progestin-only contraception	Routine pharmacovigilance	SPC section 4.5: Because ulipristal acetate binds the progesterone receptor with high affinity, it may interfere with the action of progestogen-containing medicinal products: - Contraceptive action of combined hormonal contraceptives and progestogen-only contraception may be reduced. - Concomitant use of ulipristal acetate and emergency contraception containing levonorgestrel is not recommended.
Effect in women with severe asthma insufficiently controlled by oral glucocorticoid	Routine pharmacovigilance	Use in women with severe asthma insufficiently controlled by oral glucocorticoid is not recommended.
Effects in women with impaired liver function	Routine pharmacovigilance	SPC section 4.2: Renal or hepatic impairment: In the absence of specific studies, no specific dose recommendations for Ellaone can be made. Severe hepatic impairment: in the absence of specific studies, Ellaone is not recommended.
Effects in women with impaired renal function	Routine pharmacovigilance	SPC Section 4.2: Renal or hepatic impairment: In the absence of specific studies, no specific dose recommendations for Ellaone can be made.
Efficacy and safety in repeated use	Routine pharmacovigilance	SPC: Section 4.4: Repeated administration of Ellaone within the same menstrual cycle is not advisable, as safety and efficacy of Ellaone after repeated administration within the same menstrual cycle

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimisation
		has not been investigated.

Pharmacovigilance Plan

Liver effects and effect on pregnancy maintenance will be addressed by routine pharmacovigilance, use of specific report form for spontaneous report, and special attention in PSUR. Liver effects will be labelled in section 4.4 of the SPC.

Inadvertent exposure during pregnancy: To address the inadvertent use in very early undetected pregnancy and pregnancy occurring despite correct use due to lack of efficacy, the applicant proposed the following measures in the RMP:

- Routine pharmacovigilance and post marketing data collection on pregnancy outcome in case of failure of Ellaone treatment
- A peri-postnatal study in rat (already being conducted)
- Contraindication for use in pregnancy
- Biochemical pregnancy test only in cases where a pregnancy cannot be excluded (patient history, menstrual data, symptoms or signs)
- A web-based pregnancy registry for patients and prescribers, to collect spontaneous reporting of exposed pregnancies and their outcome
- Targeting 1000 major prescribers in multiple EU countries to encourage them to enter data over approximately a 1-year period, to provide information on about 1000 pregnancies resulting from Ellaone failure
- An observational post-marketing multicenter study within a paediatric investigational plan (PIP) is being planned, and the applicant proposes to lengthen the duration of follow-up to collect more specific data about failures and pregnancy outcome.

Educational material on the registry will be agreed with the CHMP and provided to the treating physicians.
Effects in post pubertal children will be addressed by an observational study within the Paediatric Investigation Plan. For effects on pregnancy in case of treatment failure, a specific pregnancy form for spontaneous reports will be used. The effects in lactating women are addressed by SPC labelling and the excretion in milk in rats will be studied. A pharmacokinetic study in lactating women will be performed if the rat study indicates excretion in milk. Cysts will be followed by routine pharmacovigilance, special attention will be paid to ovarian cysts in PSURs and ruptured ovarian cysts will be mentioned in section 4.8 of the SPC. Concerning amenorrhoea, besides routine pharmacovigilance, special attention will be paid in PSURs and amenorrhea lasting for more than 60 days will be mentioned in section 4.8 of the SPC.

Off-label use as an abortifacient: The applicant has discussed the following options to monitor intended off-label use of Ellaone:

1. Self-reporting of prescribers,
2. Retrospective survey in Ob/gyn departments among women who are hospitalized for incomplete “spontaneous” abortions or miscarriage
3. Use of prescription registries to identify off-label prescriptions.

It is acknowledged that all these approaches suffer from similar, inevitable limitations (prescribers may not report information about off-label prescriptions). However, the applicant has responded with willingness to undertake the best efforts to evaluate the extent of such practice. In particular, the applicant will attempt to collect data from existing prescription registries on frequency and reasons for Ellaone prescriptions in individual cases, which was endorsed by CHMP. However, in order to be

meaningful, such measures will have to be implemented only when Ellaone use has reached a certain level of prescription, i.e. not before 1 to 2 years of marketing. The applicant committed to conducting a study using information from prescription registries in countries where it is considered feasible. This will be done after 1-2 years of marketing, depending on the level of Ellaone use. A protocol for such a study should be proposed by the applicant. This issue was resolved by the agreed follow up measures.

Risk Minimization Plan

The CHMP, having considered the data submitted in the application, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

2.6. Overall conclusions, risk/benefit assessment and recommendation

Quality

The Quality of this product was considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the products have been investigated and are controlled in a satisfactory way. There are a number of unresolved minor quality issues but these do not have a negative impact on the benefit/risk ratio.

Non-clinical pharmacology and toxicology

In vivo pharmacology results showed that ulipristal acetate has antiprogestinic activity shown as inhibition of progesterone induced endometrial glandular proliferation. An anti-estrogen effect of ulipristal acetate is highly unlikely.

Ulipristal acetate was shown to be effective and more potent than mifepristone in inhibiting ovulation and preventing pregnancy in rats. When given to guinea pigs and macaques at later stages of pregnancy, ulipristal acetate terminated gestation in some animals.

It was not possible to evaluate the teratogenic potential of ulipristal acetate since the doses were low in order to maintain gestation of the animals. The overall conclusion on teratogenic/embryolethal potential of ulipristal acetate is that nonclinical data overall are uncertain which is reflected in the SPC sections 4.6 and 5.3. Moreover, the SPC states that Ellaone should only be prescribed after a pregnancy test has been performed in case pregnancy is suspected.

Efficacy

Key efficacy findings

- In the controlled phase II study, non-inferiority of **50 mg unmicronized ulipristal acetate** to levonorgestrel twice 0.75 mg within 72 hours after unprotected intercourse (UPI) has been adequately shown.

- In the interim analysis of the ongoing phase III study, based on 1200 women, non-inferiority of **30 mg micronized ulipristal acetate** to levonorgestrel twice 0.75 mg within 72 hours after unprotected intercourse has been adequately shown.

- In the uncontrolled phase III study that used **30 mg micronized ulipristal acetate**, performed in women requiring emergency contraception from 48-120 hours after UPI, the primary endpoint of 'pregnancy rate' was 2.17% for the ITT Completers population. The primary efficacy analysis was performed by the applicant in a modified ITT population, but the results of the mITT population and the ITT Completers population were comparable. The observed percentage of 2.17% was significantly lower than the calculated expected pregnancy rate of 5.64% in case no emergency contraception (EC) would have been used. The method used to predict the risk of pregnancy when

no EC is administered is acceptable and widely used in studies that evaluated efficacy of levonorgestrel in this indication. When applying the conception probabilities by Trussell from 1998, almost two thirds of women (817/1241) were enrolled after intercourse that took place outside the presumed fertile window and of those 16 became pregnant. Thus, it might appear that the estimated expected pregnancy rate (risk of pregnancy) is underestimated. However, published new probability scores have lower probability scores on -4 days before ovulation up to day 0 (ovulation) than currently applied with conception probability estimations by Trussell 1998.
Nevertheless, all 1334 women took medication because of unprotected intercourse. Overall, there were 29 pregnancies (2.2%) observed. Based on Trussell's risk estimations, over the whole period, there would have been 75 expected pregnancies (5.6%). So even when bias is introduced, i.e. the extraordinary pregnancies (7 ≥ 5 days before ovulation and 9 > 1 day after ovulation), those 29 observed pregnancies (2.17%) are still much fewer than the 75 expected pregnancies (5.64%).
The observation that the hypothesized expected pregnancy rate was higher than the actual calculated expected pregnancy rate was noted in several other EC studies and therefore acceptable.
The observed pregnancy rate and the clinically most relevant secondary endpoint 'prevented fraction of pregnancies' (62%) were comparable with published pregnancy rates noted for levonorgestrel taken in the time frame 73-120 hours. The overall magnitude of the prevented fraction of 62% from day 3-5 after UPI is considered clinically meaningful.

Strength of evidence

- Efficacy 0-72 hours

Interim analysis:

- The results of the interim analysis of study HRA2914-513 showed non-inferiority of micronised ulipristal acetate 30 mg (product to be marketed) versus levonorgestrel in the 0-72 h time window. The observed pregnancy rate was numerically lower than the pregnancy rate of levonorgestrel (1.5 % vs. 2.81%) corresponding with a prevented fraction of 73% vs. the expected pregnancy rate.
  This interim-analysis was predefined in the protocol, with the condition that if the outcome of this interim analysis did satisfy the statistical criteria for efficacy as defined in the protocol, the applicant would stop recruitment in the study. This took place as of 4 February 2009. Therefore, the outcome of this interim analysis is not expected to alter the final outcome of the study, covering a total of 2048 subjects.
- Also, these interim data confirmed the initially submitted results of the phase II study showing non-inferiority between 50 mg of the unmicronised form of ulipristal acetate (initial formulation) and levonorgestrel for the same time frame of 0-72 hours. The provided additional pharmacokinetic data on dose-proportionality permit extrapolation of these results with the 50 mg unmicronised from to the final formulation of micronised ulipristal acetate 30 mg.

Therefore, it was concluded that the efficacy of ulipristal acetate as an emergency contraceptive between 0 and 72 hour after UPI had been demonstrated.

- Efficacy 72-120 hours:
  - The currently submitted study HRA2914-513 had included 214 subjects in this time window of 72-120 hours of whom only 3 were pregnant at follow-up. As this was not part of the interim analysis, no separate analysis was made between both treatment groups but based on these 3 pregnancies overall observed pregnancy rate will be low.
  - These data are in line with the results obtained for the time frame of 72-120 hours on the basis of the uncontrolled study HRA2914-501that reported an overall observed pregnancy rate of 2.1% (expected pregnancy rate of 5.5%) with separate analyses for the following time frames:

Time between intercourse and treatment (h)	Pregnancy rate (%) (n)
48 – 72	2.3 (16 /693)
73 – 96	2.0 (8 / 390)
97 – 120	1.3 (2 / 158)

- Although in the currently submitted study HRA2914-513 comparison between the observed pregnancy rates after 72-120 h is not yet possible awaiting the final analysis, these data show small differences compared to the pregnancy rates of 1.5% in the controlled trials in the time frame of 0 – 72 hours and are certainly lower than the expected pregnancy rates. Therefore, total amount of data in support of efficacy for days 72-120 since UPI is considered sufficient to accept ulipristal acetate for the whole time frame of 0-120 hours.

Safety

Regarding safety of Elleaone, adverse events were in general similar to those reported for levonorgestrel. The presence of ovarian cysts, the occurrence of amenorrhoea and the incidence of abdominal/ovarian pain were considered in line with the adverse event pattern noted for other sex hormones, including levonorgestrel. Nevertheless, these adverse events will be followed within the context of the RMP.

Although there are only few risks associated with correct use of the product, the very limited information on potential effects of treatment on a pregnancy, that may either be already existing and undetected or a result of treatment failure, needs to be further addressed within the RMP. This risk is however minimised as it is currently recommended that pregnancy should be excluded before ulipristal acetate is used and its use is contra-indicated in pregnancy.
In addition, the serious concern regarding the possibility of off-label use as an abortifacient (i.e. use of ulipristal acetate to medically terminate an already existing pregnancy) is considered adequately dealt with. The Risk Management Plan was adapted to include a plan on how off-label use will be monitored and prevented.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

Having considered the safety concerns in the risk management plan, the CHMP considered that the proposed activities described in section 3.5 adequately addressed these.

- User consultation

The applicant has submitted the results of the user testing, which was conducted in English.
The type of testing used for the readability testing of this packaging leaflet was an evaluation and problem-seeking test. The test was developed to ensure potential users of Ellaone 30mg Tablet could find, understand, and act on information given in the leaflet. A questionnaire was designed, consisting of 15 questions on the text and 4 questions that provide a positive or negative feedback from the participants for the user friendliness of the leaflet. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability.
According to the test report, each and every question was answered correctly by 100% of the participants, so therefore, no revisions of the package leaflet were proposed with respect to readability issues. It was remarked that no italics should be used in the package leaflet, except for the Latin name “Hypericum perforatum”.

Risk-benefit assessment

Efficacy has been convincingly demonstrated across the whole 120h interval. Due to the provided additional information on dose-proportionality of the unmicronized ulipristal acetate bridging of the 50 mg unmicronized formulation with the 30 mg micronized formulation it is possible, therefore, to take into account both clinical phase II studies to assess efficacy for the time frame 0-48 hours. It was also concluded that the efficacy of ulipristal acetate as an emergency contraceptive between 0 and 72 hour after UPI has been further substantiated by the submitted interim results of the ongoing study.
The applicant did not investigate the effect of multiple acts of intercourse or contraceptive failure on the pregnancy rate. Therefore, the claim “one or more acts” was removed from the indication, as this had not been specifically studied.

Regarding safety, adverse events are in general similar as reported for levonorgestrel.
Ovarian cysts, amenorrhoea, the incidence of abdominal/ovarian pain, inadverted use during pregnancy and the possibility of off-label use as an abortifacient will be followed within the context of the RMP.

The benefit-risk balance is considered positive.

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that:

- pharmacovigilance activities in addition to the use of routine pharmacovigilance were needed to investigate further some of the safety concerns.
- no additional risk minimisation activities were required beyond those included in the product information.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of Ellaone in the indication of emergency contraception within 120 hours (5 days) of unprotected sexual intercourse or contraceptive failure was favourable and therefore recommended the granting of the marketing authorisation.