CLINICAL REVIEW

Application Type	NDA
Application Number(s)	22-474
Priority or Standard	Standard
Submit Date(s)	October 14, 2009
Received Date(s)	October 15, 2009
PDUFA Goal Date	August 15, 2010
Division / Office	Reproductive and Urologic Drugs/ODE III
Reviewer Name(s)	Ronald J. Orleans, M.D.
Review Completion Date	July 27, 2010
Established Name	Ulipristal acetate
(Proposed) Trade Name	Ella
Therapeutic Class	Progesterone agonist/antagonist
Applicant	HRA Pharma
Formulation(s)	30 mg tablet
Dosing Regimen	One tablet by mouth
Indication(s)	Emergency contraception
Intended Population(s)	Women of reproductive age at risk for pregnancy

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The Applicant submitted two phase 3 studies (HRA 2914-509 and HRA 2914-513) that demonstrated that treatment with ulipristal acetate administered within 120 hours after unprotected intercourse (UPI) resulted in an observed pregnancy rate that was (1) statistically lower than the expected pregnancy rate in the absence of emergency contraception (EC) and (2) lower than the clinical relevance threshold of 4%. Similar efficacy results were observed for the primary analysis using different analysis populations (e.g., mITT, mITT2). Results of secondary efficacy analyses supported the findings of the primary analyses. No effect of age on the efficacy of ulipristal was observed. The efficacy of ulipristal remained consistent regardless of the time interval between UPI and treatment with ulipristal up to 120 hours after UPI. The effectiveness of ulipristal (as well as levonorgestrel for EC), however, appeared to be attenuated in subjects with a body mass index (BMI) > 30 kg/m^2.

Overall, in the course of a clinical development program, more than 4,700 women were exposed to ulipristal acetate, including more than 2,700 women who received the to-be-marketed 30 mg formulation. Adverse events reported during the development program were for the most part mild to moderate in severity. The most frequently reported adverse events were headache, nausea, dysmenorrhea and abdominal pain, a profile similar to that of approved emergency contraceptive products. No deaths were reported in the development program for emergency contraception. Laboratory safety parameters were measured in a subset of subjects. Changes detected after treatment were few and were not clinically significant.

At a meeting held on June 17, 2010, the Advisory Committee for Reproductive Health Drugs unanimously voted that there was sufficient safety and efficacy data to recommend marketing approval for the indication of emergency contraception up to 120 hours after unprotected intercourse. I concur with the Committee's opinion and also recommend approval of ulipristal for the indication sought.

1.2 Risk Benefit Assessment

The risk benefit ratio of ulipristal acetate for use as emergency contraception up to 120 hrs after intercourse at the dose of 30 mg appears favorable. If approved, this would be the only hormonal emergency contraceptive shown to be effective beyond 72 hours of UPI. This five day window of efficacy combined with an acceptable safety profile makes this a unique medication for the indication of emergency contraception.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

No postmarket risk evaluation and mitigation strategies are recommended.

1.4 Recommendations for Postmarket Requirements and Commitments

Data on pregnancy outcomes in subjects already pregnant prior to taking ulipristal and in subjects pregnant after EC failure with ulipristal are limited. Data is also lacking on the effect of this drug in the pediatric/ adolescent age group and in lactating women.

For this reason, the Division has determined to include postmarketing requirements as a condition if the drug is approved. The Division's recommendations can be found in Section 7.7, Additional Submissions/Safety Issues.

2 Introduction and Regulatory Background

2.1 Product Information

Ulipristal acetate (UA) is an orally-active progestrone agonist/antagonist, which is sometimes referred to as a selective progesterone receptor modulator (SPRM). UA reversibly blocks the progesterone receptors in target tissues (uterus, cervix, ovaries, and hypothalamus), inhibits ovulation and prevents pregnancy. The drug product is a tablet containing 30 mg of micronized UA. The application is submitted by HRA Pharma and the proposed tradename for the UA 30 mg tablet is "Ella." UA is a new molecular entity.

The Applicant is seeking the following indication: "Ella (ulipristal acetate 30 mg tablet) is an emergency contraceptive indicated for the prevention of pregnancy following unprotected intercourse or a known or suspected contraceptive failure."

UA was originally synthesized by Research Triangle Institute (RTI) on behalf of the United States National Institute of Child Health and Human Development (NICHD). NICHD carried out the initial preclinical and clinical development of the compound under IND 49,381.

The initial drug formulation originally developed for UA consisted of various doses of unmicronized ulipristal acetate capsules. The initial pharmacodynamic program was undertaken with these capsules, as was the phase 2 clinical trials.

HRA Pharma licensed UA (known as CDB-2914) from the NICHD and the IND was formally transferred to HRA Pharma on January 12, 2006. When HRA Pharma

became involved in the development of the product, in 2001, it sought to achieve industrial scale-up by changing the active substance manufacturing site to an industrial plant, optimizing the manufacturing process and introducing micronization as the last step of the manufacturing process, extrapolating from other hormonal products for which it is known that micronization facilitates absorption.

This background explains why, in the present application, certain studies were sponsored by NICHD rather than by HRA Pharma. The NICHD results have been made available to HRA Pharma through a collaborative research and development agreement.

On May 29, 2008, a Marketing Authorization Application (MAA) for UA 30 mg was submitted to the European Medicines Agency (EMA). The product, under the brand name EllaOne® (UA 30 mg tablet), was granted a Marketing Authorization by the EMA for emergency contraception on May 15, 2009. The Marketing Authorization is valid for the 27 European countries and is also recognized by Iceland, Lichtenstein and Norway.

Medical Reviewer's Comments

- *EllaOne is approved for marketing in 30 countries and is currently being marketed in 22 countries.*
- *UA is referred to in the literature by many different names. Among these are CDB-2914, VA2914, HRP-2000 and RTI 3021-012.*
- *If approved, UA will be the first emergency hormonal contraceptive that can be used for up to 120 hours after unprotected intercourse.*

Tables of Currently Available Treatments for Proposed Indications

In 1999, HRA Pharma's NorLevo® became the first progestin-only EC to be granted a marketing authorization in Western countries. Since that time, several preparations have been approved elsewhere in the world (e.g., Plan B®, Levonelle®, Postinor®), and currently the standard of care for EC within 72 hours of unprotected intercourse is the administration of 1.5 mg of levonorgestrel (LNG), either in a single dose or in two 0.75 mg doses taken 12 hours apart. Several countries have granted non-prescription status to these preparations based on LNG's well-characterized safety profile and limited contraindications.

Table 1 Emergency Contraceptive Regimens Approved in the US

Drug Name -Approval Date	Company	First Dose #	Second Dose #	EE per Dose (mcg)	LNG per Dose (mg)
Plan B -NDA 21-045 -approved 7/99	Teva	1 pill within 72 hours after UPI	1 pill 12 hours later	0	0.75
Plan B One-Step -NDA 21-998 -approved 7/09	Teva	1 pill within 72 hours after UPI	None	0	1.5
Next Choice -ANDA 78-665 -approved 6/09	Watson (Generic of Plan B)	1 pill within 72 hours after UPI	1 pill 12 hours later	0	0.75
Preven* -NDA 20-946 -approved 9/98	Duramed	2 pills within 72 hours after UPI	2 pills 12 hours later	0.05	0.25

*Preven is no longer available in the U.S. market.

Medical Reviewer's Comments

- *The FDA has concluded that combined oral contraceptives, taken initially within 72 hours of unprotected intercourse and providing a total of 0.10 or 0.12 mg of ethinyl estradiol and 0.50 or 0.60 mg of levonorgestrel in each of 2 doses separated by 12 hours, are safe and effective for use as postcoital emergency contraception (Federal Regist 1997;62:8610-8612).*
- *Plan B, Plan B One-Step and Next Choice are the only dedicated products specifically marketed for emergency contraception. Preven is no longer available in the U.S. market.*
- *Plan B, Plan B One-Step and Next Choice are available without a prescription to women 17 years of age and older. All three are available for women younger than 17 years of age by prescription only.*

2.3 Availability of Proposed Active Ingredient in the United States

Ulipristal acetate is a new molecular entity and is not currently available in any U.S. approved product.

2.4 Important Safety Issues with Consideration to Related Drugs

Safety issues with related drugs relate pertain exclusively to mifepristone, because there is only very limited clinical experience with other SPRMs. Because of its specific action at the progesterone and glucocorticoid receptors, serious adverse effects are rare and mifepristone is generally well tolerated.

Deaths and serious infections possibly related to mifepristone/misoprostol use for pregnancy termination have been reported.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Ulipristal acetate was developed under an investigational new drug (IND) application, IND 49,381, which was opened in 1995 and transferred from NICHD to HRA Pharma effective January 12, 2006. Various meetings were held with both IND holders dating back to 1996.

In 1996, the Agency reviewed the available toxicology and phase 1 trial results and provided guidance on the preclinical studies to be carried out and the design requirements of necessary phase 2 and 3 efficacy trials. The proposed phase 2/3 protocol and clinical development program were discussed again in 1998.

An end of phase 2 meeting was held on April 19, 2004 with NICHD. At this meeting, the Division suggested that two adequate and well-controlled studies are generally required for a new molecular entity and stated that a comparative study against an approved emergency contraceptive drug would be preferred to an open-label study. Although the Division agreed that subjects could be enrolled up to 120 h after unprotected intercourse, primary efficacy was to be based upon the 72-hour timeframe because of the limitation in the approved product. In addition, the Division recommended that at least a 50% of the subjects in the phase 3 trials be from US centers.

HRA submitted a Special Protocol Assessment Request for two phase 3 protocols, 2914-004 and 2814-005, to the Division on April 20, 2006. The Division reviewed the protocols and provided written responses to the Applicant's questions on June 8, 2006.

A meeting was held on July 25, 2006 to discuss the Division's recommendations. At this meeting, there was agreement regarding proposed primary efficacy endpoints and the proposed analysis populations for each protocol. The Division was also in agreement regarding the proposed definition of success for each study, i.e., success would be declared if:

- the observed pregnancy rate was statistically significantly lower than the estimated pregnancy in the absence of EC and
- that the upper bound of the two sided CI was less than the clinically meaningful threshold of 4%.

A subsequent pre-NDA meeting was held on December 12, 2008 to discuss the format and contents of the NDA submission for ulipristal acetate for the indication of EC. The definition of noncompatible (with drug failure) pregnancies was discussed. In addition, the Applicant was asked to address in the NDA application how ulipristal can be safely made available under non-restrictive conditions while at the same time guarding against the possibility of off- label use as a possible abortifacient.

2.5 Other Relevant Background Information

Progesterone is essential for the initiation and maintenance of pregnancy. After the discovery of the progesterone receptor (PR) in 1970, it was realized that a progesterone receptor antagonist would have a major impact on female reproductive health. In 1981, a synthesized glucocorticoid receptor antagonist known as RU 38486 was described. It soon became evident that this antiglucocorticoid also displayed marked antiprogestin activity. RU 38486 was subsequently abbreviated to RU 486 and is now known by the generic name mifepristone.

Since the discovery of mifepristone, several hundred similar compounds have been synthesized. These compounds may display progestrone agonist, antagonist or mixed agonist/antagonist activity and thus function as progesterone receptor agonists, progesterone receptor antagonists, or selective progesterone receptor modulators (SPRMs), respectively. SPRMs represent a class of progesterone receptor ligands that exerts clinically relevant, tissue selective, mixed progesterone agonist and antagonist effects, which may be full or partial, on various progesterone target tissues in an *in vivo* situation depending on the biological action studied.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

This was an electronic submission. The quality of the overall submission was adequate for review.

3.2 Compliance with Good Clinical Practices

The clinical investigator sites of Dr. William Casale (Sites 39 and 42) and Dr. Savita Ginde (Sites 7 and 9) and the Applicant, Laboratoire HRA Pharma, were inspected in support of this NDA.

Medical Reviewer's Comments

- *The clinical sites were selected for inspection because of their high enrollments.*
- *The Applicant inspection is standard for a new molecular entity.*

At Dr. Casales' site 42, the records of 60 subjects were audited. The inspection revealed that Subjects 005 and 007 were randomized to treatment despite having unprotected intercourse more than 120 hours prior to requesting emergency contraception. In addition, Subjects 003, 004, 008, 011, 026, 116, and 124 were enrolled in the wrong window treatment group because of the site's error in calculating the time window between treatment intake and unprotected intercourse (within 72 hours and between 72-120 hours). A Form FDA 483 was issued at the conclusion of the

inspection. At site 39, the records of 40 subjects were audited. The inspection of site 39 revealed that two subjects (024 and 065) did not meet the inclusion criterion of regular menstrual cycles as required by the protocol, and that Subject 038 was enrolled in the study and received the test article despite not having a required blood sample drawn prior to treatment. In addition, Subjects 002 and 058 were enrolled in the wrong window treatment group because of the site's error in calculating the time window between treatment intake and unprotected intercourse (within 72 hours and between 72-120 hours).

DSI's overall assessment of data integrity for each of these sites concluded "The review division may wish to consider the impact, if any, of data derived from the subjects noted above. Otherwise, the study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication."

Medical Reviewer's Comment

- *The FDA statistician reviewed the DSI findings and concluded that the errors in calculating the time window between UPI and treatment intake did not impact the FDA analysis because the FDA statistician independently calculated these time intervals and did not rely on the Applicant's data in that regard.*

The inspection of Dr. Gindes' two sites did not reveal any significant discrepancies or regulatory violations. A Form FDA 483 was not issued at the conclusion of the inspection.

The Applicant's study activities with regard to, but not limited to, organization and personnel, selection and monitoring of clinical investigators and monitors, quality assurance, adverse event reporting, automated data entry, and test article accountability were evaluated. DSI concluded that "Data appear acceptable in support of the respective application" and that "no significant regulatory violations were noted." A Form FDA 483 was not issued.

DSI concluded that the study appears to have been conducted adequately, and the data generated by the clinical sites of Drs. Casale and Ginde appear acceptable in support of the respective indication.

3.3 Financial Disclosures

The Applicant has signed Form FDA 3454 stating that:
(1) HRA has not entered into any financial arrangement with the listed clinical investigators whereby the value of compensation to the investigator could be affected by the outcome of the study.
(2) No listed investigator disclosed had a proprietary interest in this product or a significant equity in HRA.

(3) No listed investigator was a recipient of significant payments from HRA.

Medical Reviewer's Comment

- *None of the clinical investigators involved in the phase 3 trials HRA 2914-513 and HRA 2914-509 and in the phase 2 trials HRA 2914-507 and HRA 2914-508 had anything to disclose.*

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The drug product is a non-coated tablet indicated for emergency contraception for up to 120 hours and it contains 30 mg of ulipristal acetate. The drug product is manufactured (b) (4) are considered to be critical operations, and they are deemed well controlled with acceptable operating ranges.

The Applicant provided the results of 24 months long-term stability studies and there were no significant changes observed in the stability lots.

Medical Reviewer's Comments

- *The CMC reviewer has determined that the Applicant has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product.*
- *The CMC reviewer stated in his review that "Adequate controls for raw materials are in place; manufacturing processes are robust and adequately controlled; and the specifications are adequate for ensuring the identity, strength, quality, and purity of the drug substance and the drug product. Adequate container/closure system is in place to protect the drug product during the storage. Sufficient stability data are provided to allow 36-month of the expiration dating period*
- *An overall "Acceptable" site recommendation has been made from the Office of Compliance.*

4.2 Clinical Microbiology

No microbiology issues were identified.

4.3 Preclinical Pharmacology/Toxicology

Generalizability of the nonclinical study findings to human use is limited for several reasons.

- The effects of the drug are species-, dose-, duration-, and time-dependent
- Most studies examined higher doses than the human dose
- The potential for pregnancy termination by a single dose of UA was not assessed
- No study evaluated the effects of administration during the period of time immediately following implantation

A summary of the nonclinical findings regarding the potential adverse effects on human pregnancy are as follows:

- There is limited animal data due to few surviving offspring at clinically relevant dose exposures.
- No malformations were noted in any offspring of treated rats, rabbits and monkeys
- UA was not genotoxic based on standard *in vitro* and *in vivo* assays.

Medical Reviewer's Comments

- *Pharmacology/Toxicology data is limited regarding the abortifacient activity of this drug or the effect of the drug on a human fetus.*
- *The Pharmacology/Toxicology reviewer recommended approval the indication sought. He summarized his review as follows: "Overall, the pharmacology, pharmacokinetics, and toxicology effects of CDB-2914 were consistent between rats and monkeys and were similar to the effects seen in humans. CDB-2914 is a potent antiprogestin with anti-glucocorticoid activity and most of the nonclinical findings in the toxicology studies appear to be due to exaggerated antihormone pharmacology of CDB-2914. The nonclinical reproductive toxicology findings suggest that there is a fetal risk if this drug is administered to a pregnant woman, specifically interruption of an established pregnancy. The ability to interrupt an established pregnancy with a single dose was not directly investigated in the pivotal nonclinical studies, but the data from published reports and one reproductive toxicology study (GD17-19 dosing at 4x the human dose based on mg/m2) suggest that the potential exists. From a pharm/tox perspective, the nonclinical data support approval for emergency contraception."*

4.4 Clinical Pharmacology

NICHD developed a drug formulation for UA that consisted of capsules of various doses of unmicronized ulipristal acetate. The initial pharmacodynamic program was undertaken with these capsules, as were the phase 2 clinical trials. When HRA Pharma became involved in the development of the product in 2001, it sought to achieve industrial scale-up by changing the active substance manufacturing site to an industrial

plant, optimizing the manufacturing process and introducing micronization as the last step of the manufacturing process, extrapolating from other hormonal products for which it is known that micronization facilitates absorption.

Medical Reviewer's Comment

- *The bioavailability of micronized ulipristal appeared to be 40% greater than that of non-micronized ulipristal. This is further discussed in Section 4.4.3 Pharmacokinetics*

Following a single dose administration of ulipristal acetate 30 mg micronized tablet in healthy women under fasting conditions, the maximum plasma concentrations (C_{max}) of ulipristal and its active metabolite, 3877A, were reached within 1 hour of administration (range, 0.5 – 2 hours). The mean (±SD) C_{max} values of ulipristal and metabolite 3877A were 176.0 ± 51 and 68.6 ± 38 ng/mL, respectively, The mean (±SD) area under the curve (AUC) values were 556.0 ± 47 and 246.0 ± 24, respectively. The C_{max} and AUC of ulipristal acetate were more than twice the values of those of the 3877A (HRA 2914-504).

The C_{max} and AUC of ulipristal acetate and 3877A following a single dose administration of 10 mg micronized tablet were higher compared to those from a 10 mg unmicronized capsule (HRA 2914-501).

In vitro data indicate that the metabolism of ulipristal acetate is predominantly mediated by CYP3A4. Concomitant administration of CYP3A4 inhibitors may inhibit the metabolism of ulipristal acetate and cause increased plasma concentration of ulipristal acetate. In addition, concomitant administration of CYP3A4 inducers may reduce plasma concentrations of ulipristal acetate and may result in decrease in efficacy.

Medical Reviewer's Comment

- *The Division of Clinical Pharmacology determined that the clinical pharmacology information submitted was acceptable provided that an agreement is reached between the Applicant and the Division regarding the language in the package insert.*

4.4.1 Mechanism of Action

Based on the findings of the pharmacodynamic studies, UA appears to inhibit or delay ovulation, depending on the time of administration in the follicular phase. When given in the luteal phase, UA may exert an anti-progesterone effect on the endometrium also depending on the dose and time of drug administration.

Medical Reviewer's Comments

- *No single mechanism of action has been established for emergency contraception. The mode of action may vary according to the day of the*

menstrual cycle on which intercourse occurs and the day the medication is administered.

- *Based on the phase 1 data, the primary mechanism of action of Ella when taken prior to or at the time of ovulation appears to be inhibition or delay of ovulation (even after the onset of the LH surge), depending on the time of administration in the follicular phase. Another possible mechanism of action is delaying the maturation of the endometrium in the luteal phase of the menstrual cycle due to the drug's antiprogestrone effect. This delay of maturation may result in prevention of implantation.*
- *We do not have any information regarding the possible effect of Ella on tubal transport of sperm and/or ova.*
- *Levonorgestrel also acts by interfering with the luteinizing hormone peak but does not seem to interfere with the ovulatory process as efficiently as ulipristal especially when levonorgestrel is taken close to ovulation. The product label for Plan B One-Step (levonorgestrel 1.5 mg) states that the product "is believed to act as an emergency contraceptive principally by preventing ovulation of fertilization (by altering tubal transport of sperm and/or ova). In addition, it may inhibit implantation (by altering the endometrium). It is not effective once the process of implantation has begun."*
- *Lastly, because Ella is more effective than Plan B when given more than 72 hrs after unprotected intercourse, this may indicate (albeit unproven) that Ella has a greater effect on the endometrium when given after ovulation and thereby a greater potential for preventing implantation.*

4.4.2 Pharmacodynamics

The effect of single doses of UA on ovulation and endometrial maturation was evaluated in four phase 1 studies in healthy women volunteers with normal menstrual cycles. Three of these 4 studies (HRA 2914-503, HRA 2914-504, and HRA 2914-506) were sponsored by the NICHD and investigated single doses ranging from 0 to 200 mg of unmicronized UA administered at different phases in the menstrual cycle (mid-follicular, early luteal, or mid-luteal). Study HRA 2914-511, sponsored by HRA Pharma, evaluated the effect of a single dose of the to-be-marketed formulation of ulipristal (30 mg micronized tablet) administered in the late follicular phase. Pertinent findings follow:

- Mid-follicular phase (HRA 2914-505): Ulipristal suppressed growth of the lead follicle and delayed ovulation at 50 and 100 mg doses. Inhibition of luteal phase endometrial maturation was observed at all dose groups (10, 50 or 100 mg unmicronized).
- Late follicular phase (HRA 2914-511): Administration of ulipristal (30 mg micronized) immediately before ovulation (when follicular rupture is imminent) showed an inhibitory effect on follicular rupture in a majority of cycles (11/14 subjects, 80%), even when given after the onset of the LH surge.

- Early luteal phase (HRA 2914-506): Ulipristal delayed endometrial maturation at higher doses tested (50 and 100 mg unmicronized) without affecting luteolysis or menstrual cycle length.
- Mid-luteal phase (HRA 2914-503): No significant effect on menstrual cycle length was observed at unmicronized doses up to 100 mg. However, subjects receiving a single 200 mg unmicronized dose all had a shortened luteal phase, early menses, and prolonged bleeding, indicating a direct action on the endometrium.

4.4.3 Pharmacokinetics

The Applicant studied micronized and non-micronized formulations of UA. Following single dose administration of the ulipristal 30 mg micronized tablet, the mean plasma concentrations of ulipristal and its major metabolite 3877A reached a peak within one hour of administration. Maximum plasma concentrations and exposures to ulipristal were approximately one half that of the metabolite.

Dosing with food reduced the rate of absorption of ulipristal, as indicated by a 40-45% lower maximum plasma drug concentration (Cmax) and by a delay in time to Cmax (Tmax) of about 1.5 hour for both ulipristal and 3877A. Food intake, however, increased the extent of absorption, as indicated by 20-25% higher AUC for ulipristal and 3877A compared to dosing under fasting conditions. Phase 3 studies (HRA 2914-509 and HRA 2914-513) were conducted without restriction for food. Therefore, ulipristal acetate can be administered regardless of food intake.

The pharmacokinetic bridging study of three different drug formulations at the same dose was undertaken (crystalline unmicronized drug in capsules, micronized drug in capsules, and micronized drug in tablets) in Study HRA 2914-501. The results showed that in comparison with the unmicronized capsule, the micronized tablet formulation was absorbed faster, had a plasma concentration peak nearly two-fold higher, and had a relative bioavailability of 1.44. Based on pharmacokinetic considerations, in order to obtain an efficacy and safety profile similar to what was observed with the 50 mg formulation, a dose of 30 mg micronized drug substance formulated in a tablet was chosen.

5 Sources of Clinical Data

5.1 Table of Clinical Trials

The efficacy of UA for emergency contraception was evaluated in several phase 2 and phase 3 clinical trials.

Table 2 Phase 2 and Phase 3 Clinical Development Program

Study Number	Primary Objective	Ulipristal acetate/ Comparator	Protocol Number Design	Sponsor
HRA 2914-507 • Phase 2 • 9/20/99 to 9/10/01 • 7 US sites • N=1672 enrolled	Efficacy, safety compared to LNG[a] taken within **0-72 hrs** of UPI[b]	-UA[c] 50 mg unmicronized capsule, single dose/ -LNG 0.75 mg, 2 doses taken 12 hours apart	Protocol CCN002-01 -Double-blind, controlled -UA 50 mg arm: n=832 -LNG 0.75 mg x 2 arm: n=840 -4 week follow-up	NICHD
HRA 2914-508 • Phase 2 • 8/20/01 to 11/6/03 • 9 US sites • N=1026 enrolled	Efficacy, safety of two different doses taken within **0-72 hrs** of UPI	-UA 50 mg unmicronized capsule -UA 10 mg unmicronized capsule initially[d] then changed to UA 10 mg micronized capsule	Protocol CCN002-02 -Double-blind, controlled -UA 10 mg micronized: n= 399 -UA 50 mg unmicronized: n=413 -4 week follow-up	NICHD
HRA 2914-509 • Phase 3 • 11/27/06 to 3/31/08 • 45 US sites • N=1533 treated	Efficacy, safety of single dose taken within **48–120 hrs** of UPI	**-UA 30 mg micronized tablet (Single dose final formulation)**	Protocol 2914-005 -Open-label, single arm -4 week follow-up	HRA Pharma
HRA 2914-513 • Phase 3 • 4/9/07 to 4/2/09 • 35 sites: US: 24 UK: 10 Ireland: 1 • N=2221 treated	Pregnancy rate of single dose taken within **0-120 hrs** of UPI	-**UA 30 mg micronized tablet (Single dose final formulation)** -Levonelle® 1.5 mg tablet, single dose	Protocol 2914-004 -Single-blind, randomized -UA 30 mg: n=1104 -LNG 1.5 mg: n=1117 -4 week follow-up	HRA Pharma

[a] LNG: Levonorgestrel
[b] UPI: Unprotected intercourse
[c] UA: Ulipristal acetate
[d] Treatment group discontinued due to lack of efficacy

5.2 Review Strategy

Clinical review strategy involved a review of the four individual clinical study reports from Studies HRA 2914-507, HRA 2914-508, HRA 2914-509 and HRA 2914-513. The proposed label was also reviewed.

Previous meeting minutes and agreements between the Division and the Applicant were also reviewed.

During the course of this review, the Applicant was asked to provide additional clinical information for review.

On 12/23/2009, the Division issued a 74-Day letter containing the following information requests:

1. Provide all information about any post-marketing activities requested by the "European Commission," including further information about the pregnancy registry noted in the Summary of Product Characteristics (SPC). Any pregnancy outcome data available in this registry should be submitted at the time of the 120-day safety update.
2 Provide further information on the likely mechanism of action of ulipristal when used as an emergency contraceptive. Clarify the difference between the proposed US label and the SPC.

The Applicant responded to the above questions on 1/19/2010 (SDN 006).

1. Nine specific "post-authorization activities" were requested by the European Medicines Agency. These activities included:
    - The Applicant will undertake a study investigating the pharmacokinetics of UA in healthy breastfeeding women who take 30 mg and the amount of drug transferred into human milk.
    - The Applicant will submit a protocol for the pregnancy registry before launch of the product. The pregnancy registry strategy will include educational material to be distributed to treating physicians to inform them of the existence and use of the registry.
    - The Applicant commits to conduct a study targeting 1000 prescribers in multiple EU countries to obtain clinical follow-up information on pregnancies exposed to UA or resulting from UA failure.
    - The applicant commits to conduct a study to identify off-label prescriptions 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 UA use.
2. A summary of the Applicant's response to Question 2 is as follows:

Ulipristal acetate's mechanism of action in emergency contraception has been elucidated in their pharmacodynamic studies; most recently study HRA 2914-511

(Complete Study Report dated 28 July 2009). As study HRA 2914-511 was only completed post-authorization in the European Union, the results were only recently submitted to the European Medicines Agency and are currently being evaluated. These data were not taken into account when the first Summary of Product Characteristics (SPC) was approved in May 2009. The description of the likely primary mechanism of action of UA in the proposed SPC exactly reflects the proposed US label submitted to the FDA.

The ability of UA to delay or inhibit follicular rupture in a dose-dependent fashion with administration in the mid-follicular phase was demonstrated by the NIH early in the compound's clinical development. This most recent study (HRA 2914-511) provides evidence that UA delays follicular rupture with administration very late in the follicular phase, which is the time in the cycle when the probability of conception peaks. In brief, the results of this study show that after giving UA very late in the follicular phase, even when Luteinizing Hormone (LH) levels have already started to rise (LH<15.6 IU/mL), the lead follicle is still present on ultrasound 5 days after treatment intake in a significant proportion (11/14, 78.6%) of subjects. This observed high rate of inhibition of follicular rupture when administered immediately before the LH peak can thus be considered as the primary mechanism underlying the observed prevention of pregnancy in clinical trials. Similarly-designed pharmacodynamic studies published for LNG emergency contraception showed that if administered well before the onset of the LH surge it exerted inhibitory effects on ovulation via shunting of the LH surge, but that it does not significantly delay or inhibit follicular rupture when administered in the advanced preovulatory phase. Therefore, the observed improved efficacy with UA as compared with levonorgestrel administered for emergency contraception can also be attributed to this inhibition of follicular rupture.

5.3 Discussion of Individual Studies/Clinical Trials

The phase 2 program was sponsored by NICHD and included two double-blind studies performed in the US within the NICHD contraceptive clinical network: the first one (HRA 2914-507) compared a single 50 mg dose of unmicronized UA with two 0.75 mg doses of levonorgestrel and the second one (HRA 2914-508) compared 50 mg vs. two formulations each containing 10 mg ulipristal acetate for contraceptive efficacy.

Medical Reviewer's Comments

- *The phase 2 program provided evidence for several important findings:*
  - *UA formulated at the dose of 50 mg unmicronized in a gelatin capsule was safe and effective for emergency contraception.*
  - *UA micronized and formulated at the dose of 10 mg in gelatin capsule was more efficacious for emergency contraception than UA unmicronized and formulated at the dose of 10 mg, which indicated that micronization of the drug substance improved clinical efficacy.*
  - *UA micronized and formulated at the dose of 10 mg in a gelatin capsule was less efficacious for emergency contraception than UA unmicronized formulated at the dose of 50 mg in a gelatin capsule.*

The Applicant completed two phase 3 studies. Both studies provide support for safety and efficacy of ulipristal for EC from 0 to 120 hours after UPI. Study HRA 2914-509 was an open-label trial conducted in the US with the primary objective of evaluating the efficacy of a single 30 mg oral dose of ulipristal for EC when used between 48 to 120 hours after UPI. Study HRA 2914-513 was a randomized, single-blind trial conducted in the US and Europe with the primary objective of evaluating the efficacy of a single 30 mg dose of ulipristal for EC, taken between 0 and 72 hours after UPI, compared to that of a single dose of 1.5 mg LNG.

Phase 3: HRA 2914-509

Title:
"A Prospective, Open-Label, Single Arm, Multicenter Study to Evaluate the Efficacy, Safety and Tolerability of CBD-2914 as Emergency Contraception When Taken Between 48 Hours and 120 Hours of Unprotected Intercourse"

Study Objectives
The primary objective of the study was to demonstrate that the pregnancy rate observed after taking UA 30 mg between 48 hours and 120 hours after UPI was statistically significantly lower than the estimated expected pregnancy rate in the study population in the absence of emergency contraception.

Secondary objectives were to (1) demonstrate that the pregnancy rate observed after taking UA 30 mg between 48 and 120 hours after unprotected intercourse was statistically significantly lower than 4% clinical relevance threshold, (2) to analyze the trend in pregnancy rates over time from the time of UPI and to estimate the contraceptive effectiveness (prevented fraction) of UA 30 mg.

Medical Reviewer's Comment

- *The clinical relevance threshold of 4% represents a reduction by half of the expected 8% pregnancy rate in the absence of contraception that has been*

observed in previous studies. The 4% threshold was thought by the Applicant to represent a clinically meaningful reduction in the pregnancy rate.

Demonstrating the safety, tolerability and the impact of UA on menstrual cycle length was also a secondary objective.

Trial Design

Trial 2914-509 was a prospective, open-label, single-arm trial designed to evaluate the efficacy, safety and tolerability of a single dose of UA 30 mg taken orally 48 to 120 hours after UPI. The trial was conducted at 40 Planned Parenthood family planning clinics, all located in the United States. A total of 1,623 subjects, ages 18 years and older, who presented for emergency contraception at 48 to 120 hours after UPI and who met the inclusion/exclusion criteria were screened.

Women at least 18 years of age, with regular menstrual cycles (between 24 and 35 days), who presented requesting EC between 48 and 120 hours after UPI and met other inclusion/exclusion criteria were enrolled into the study after they signed the informed consent form.

Medical Reviewer's Comment

- *As no emergency contraceptive is currently approved to be taken more than 72 hours after UPI, no active control was used in this study.*

Significant inclusion criteria were regular menstrual cycles 24–35 (±5) days in length, no current use of hormonal contraception, willingness not to use hormonal contraception until study completion, and agreement to use barrier methods of contraception from enrollment to study completion. Significant exclusion criteria included pregnancy, breastfeeding, IUD, tubal ligation or a partner with a vasectomy, and uncertainty about recent menstrual history.

A total of up to three visits were scheduled over the course of the study: treatment visit Day 1 was the screening phase, and treatment phase. This was followed by up to two subsequent visits. Prior to study drug administration on Day 1, pregnancy status was verified by a high sensitivity urinary pregnancy test (HSUP]) and a blood sample was taken and stored for potential serum β-hCG pregnancy testing at a later date, if necessary. The study medication, a single dose of UA 30 mg, was administered on Day 1 after all eligibility criteria, including a negative urine pregnancy test, were verified.

Medical Reviewer's Comments

- *The pre-dose serum β-hCG was obtained in order to help exclude a pregnancy that predated study drug intake from the count of pregnancies that represented EC failure.*
- *The HSUP test has a level of detection of β-hCG of ≥ 20 mIU/mL.*

At the first follow-up visit (5-7 days after expected onset of menses), a HSUP test was performed. Further study procedures depended on the following outcome of this urinary pregnancy test:

- Negative HSUP and resumption of menses: study completion procedures were performed.
- Positive HSUP: a serum β-hCG was performed and if positive, the frozen pre-treatment serum was also analyzed to determine if the subject was pregnant prior to treatment. A transvaginal ultrasound (TVUS) was then scheduled for more accurate dating of the day of conception. A pregnant subject was to be followed until the pregnancy outcome was determined.
- Negative HSUP but no resumption of menses: a second follow-up visit was scheduled one week later (12-14 days after the expected onset of menses). The procedures from the first follow-up visit were then repeated. If the repeat HSUP test was negative and menses still had not returned, a serum β-hCG was performed. If still negative, the subject was entered into an amenorrhea follow-up phase and contacted every two weeks with periodic pregnancy testing until return of menses. If menses had not returned by 60 days, a secondary amenorrhea work-up was initiated. This work-up included serum levels of thyroid-stimulating hormone, follicle-stimulating hormone, luteinizing hormone, estradiol, prolactin, a progestin challenge test, and ultrasonography.

Subjects kept a home diary calendar from the time of treatment until study completion, in which they recorded further acts of intercourse during the cycle, vaginal bleeding, concomitant medication use, and occurrence of adverse events.

Medical Reviewer's Comment

- *A summary of the protocol for this trial can be found in Appendix 1.*

Women could enroll in the study more than once, but they must have completed the prior study participation before reenrolling. Safety laboratory testing was performed for all women repeating enrollment.

A Data Safety Monitoring Board (DSMB) was set up, consisting of two experts in the field of gynecology to assess whether each pregnancy was "compatible" or "not compatible" with EC failure. This determination was made based on pre-treatment serum beta HCG level and gestational age confirmed by transvaginal ultrasound.

Medical Reviewer's Comments

- *Sperm have been shown to live for no longer than 6 days in the urogenital tract. Therefore, an act of intercourse may potentially lead to fertilization up to 6 days later.*
- *Based on the reported date(s) of unprotected intercourse having led to EC intake, the DSMB constructed a fertilization window that included the date of UPI plus 6 days. If the estimated fertilization date, as determined by the DSMB,*

overlapped with the fertilization window, the pregnancy was considered a treatment failure. If the fertilization date did not overlap with the fertilization window, the pregnancy was considered not compatible with an EC failure. In such case, the DSMB determined the most probable conception date based on other available data (LMP, cycle length, all acts of intercourse in the cycle).

Primary Efficacy Measurement and Analysis

The primary efficacy measurement was the pregnancy rate, defined as the number of pregnancies after administration of UA for EC divided by the number of women treated and whose pregnancy status was known.

The primary efficacy analysis compared this pregnancy rate to the pregnancy rate that would have been expected in the absence of EC treatment, which was calculated according to the method of Trussell (Trussell J, et al. Contraception 1998; 57:363) using the set of conception probabilities and the estimated cycle day of UPI based on the subject-reported date of last menstrual period, cycle length, and date of UPI.

The observed pregnancy rate was considered to be statistically significantly lower than the expected pregnancy rate if the upper bound of the two-sided 95% confidence interval (CI) around the observed pregnancy rate was below the estimated expected pregnancy rate. The protocol also stipulated that both the primary and main secondary efficacy analyses (upper bound of the 95% CI less than 4%) needed to be positive for the study to be considered a success.

A pregnancy was documented by a positive HSUP test after emergency contraception intake. Pregnancy status (yes/no) was determined as follows:

- Yes: positive HSUP confirmed by a positive quantitative serum β-hCG at Follow-up Visit 1 or 2
- No: if the HSUP was negative and menses resumed at Follow-up Visit 1 or 2, or if menses had not resumed at Follow-up Visit 2 and the quantitative serum β-hCG was negative, or as assessed by the investigator based on available information at follow-up.

The cycle day of UPI (cycle day relative to day of ovulation) for each subject was determined as follows:

Cycle day of UPI = (Date of UPI – Date of first day of last menstrual period + 1) – (Average length of menstrual cycle – 14).

The pregnancy was determined to be compatible or incompatible with EC failure based on the independent evaluation by the DSMB. A pregnancy was classified as not compatible with drug failure if it was identified as having started before EC intake or if the estimated date of conception was outside the fertile window.

The probability of conception for each cycle day of UPI (relative to ovulation) was determined from the data displayed in Table 3.

Table 3 Probability of Conception Based on Cycle Day of UPI

	Cycle Day of Unprotected Intercourse								
	<-5	-5	-4	-3	-2	-1	0	+1	>+1
Probability of Conception	0.0%	3.6%	13.6%	15.5%	27.7%	29.8%	12.3%	4.5%	0.0%

Source: Trussell J, Rodriguez G, Ellertson C. New Estimates of the Effectiveness of the Yuzpe Regimen of Emergency Contraception. Contraception 1998; 57:363–9.

Medical Reviewer's Comments

- *The expected pregnancy rate (in the absence of a 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 the pregnancy rate to no more than half of this pregnancy rate (4%) is considered by the Applicant to be clinically meaningful for an EC method.*
- *The estimated day of fertilization and the fertile window of - 5 to +1 days were calculated based on the subject's diaries, menstrual cycle length and on transvaginal ultrasonography.*

In the event that a subject had multiple acts of UPI before treatment with UA during the cycle, the conception probability used in the analysis was that of the act of intercourse carrying the greatest conception probability. Intercourse was determined to be unprotected if contraception was not used or was used but failed for some reason.

Main Secondary Efficacy Analysis

The main secondary efficacy analysis was the determination of non-inferiority of the observed pregnancy rate in subjects treated with ulipristal compared to the Applicant's clinical relevance threshold of a 4% pregnancy rate. Ulipristal was to be declared non-inferior to this clinical threshold if the upper limit of the 2-sided 95% CI of the observed pregnancy rate was lower than 4%.

The clinical trial was to be considered as a success if both the primary efficacy analysis and the main secondary analysis (non-inferiority to the clinical relevance threshold of 4%) demonstrated efficacy in the mITT population, based on subjects who used ulipristal between 48 hours and 120 hours after UPI.

Medical Reviewer's Comment

- *Because the Applicant's statistical analysis plan specified that the study would be considered a success if both the primary efficacy analysis and main secondary efficacy analysis were successful, the Division considered both of these analyses as co-primary analyses.*

Additional Secondary Efficacy Analyses

1. Prevented fraction of pregnancies. The prevented fraction of pregnancies was defined as the number of prevented pregnancies divided by the number of estimated expected pregnancies, where the number of prevented pregnancies was calculated as follows:

   - Number of prevented pregnancies = Number of estimated expected pregnancies minus the number of observed pregnancies

   The number of estimated expected pregnancies was determined based on conception probabilities by cycle day of UPI as described previously.

2. Trend in pregnancy rates over time**.** Pregnancy rates, based on the actual time between UPI and the subject's taking ulipristal, were calculated for each 24-hour period over the interval ranging from 48 hours to 120 hours.

Analysis Populations

The Applicant's definitions of different analysis populations included:

1. Intent-To-Treat (ITT) Population (also the Safety Population) consisted of all subjects who received emergency contraception. Repeat enrollers were included and treated as independent subjects in the analysis.
2. ITT Completers consisted of all ITT subjects who met the following criteria:
   - Participating for the first time in the current study (i.e., repeat enrollers were not included);
   - With a known pregnancy status after EC intake (as stated by the investigator in the study completion form).
3. Modified Intent-To-Treat (mITT) Population consisted of all ITT Completers who met the following criteria:
   - Age ≤ 35 years;
   - Pregnancy NOT identified as having been conceived before EC intake (as measured by pre-treatment serum β-hCG level and gestational age confirmed by transvaginal ultrasound [TVUS]) or as "not compatible" with an EC failure, based on independent evaluation by the DSMB. (In addition to serum HCG levels, the DSMB used additional criteria such as TVUS, LMP, cycle length, all acts of intercourse in the cycle, and date of EC use to make its determination that a pregnancy was not compatible with failure of the study drug to prevent the pregnancy.)
4. Modified Intent-To-Treat-2 (mITT2) Population consisted of all mITT subjects, but also **included** those subjects whose pregnancies the DSMB considered "not compatible" with an EC failure.
5. Per Protocol (PP) Population consisted of mITT completers who did not have major protocol violations, including intake of hormonal contraception or UPI after EC intake during the study treatment cycle.

Efficacy analyses were performed by the Applicant on the mITT, mITT2, ITT completers, ITT, and PP populations. The Applicant considered the mITT population the primary efficacy analysis population.

Medical Reviewer's Comment

- *The Division also considered the Applicant's mITT population to be the primary efficacy analysis population. However, the Division independently reviewed all pregnancies classified by the DSMB as "not compatible" with an EC failure. In some instances, the Division did not believe that the data warranted exclusion of a subject from the primary efficacy population. Therefore, this later population, referred to as the "FDA efficacy population" in this document, was used in the Division's assessment of efficacy.*

Phase 3 HRA 2914-513

Title
"A Prospective, Randomized, Single Blind, Multicenter Study to Compare the Efficacy, Safety and Tolerability of CDB-2914 with Levonorgestrel as Emergency Contraception within 120 Hours of Unprotected Intercourse"

Trial Objectives
The primary objective of the study was to demonstrate that the pregnancy rate observed after UA 30 mg taken within 72 hours of UPI was significantly lower than the estimated expected pregnancy rate in the absence of emergency contraception.

Principal secondary objectives were:

- Provide evidence that the pregnancy rate observed after taking UA 30 mg within 72 hours of unprotected intercourse is lower than the Applicant's clinical relevance threshold of 4%.
- Provide evidence of the non-inferiority of UA 30 mg versus LNG 1.5 mg as EC within 72 hours of UPI. Should non-inferiority be demonstrated, superiority would be tested.
- Provide evidence that the pregnancy rate observed after taking UA 30 mg within 120 hours of UPI is lower than the expected pregnancy rate in the absence of EC.
- Provide evidence that the pregnancy rate observed after taking UA 30 mg within 120 hours of UPI is lower than the clinical relevance threshold of 4%.
- Evaluate the trend in pregnancy rates over time since intercourse after UA 30 mg or LNG 1.5 mg.
- Assess the Prevented Fraction in both treatment groups.
- Assess and compare the impact of UA 30 mg and LNG 1.5 mg on the menstrual cycle.
- Evaluate the safety and tolerability profile of UA 30 mg in comparison to LNG 1.5 mg.

Trial Design

This was an international, prospective, multicenter, randomized, single-blind (subject and sponsor blinded, investigator unblinded), parallel arm study designed to evaluate the efficacy, safety, and tolerability of a single dose of ulipristal 30 mg compared to a single dose of LNG 1.5 mg administered for EC within 120 hours after UPI. The study was conducted in 11 centers in Europe and 24 centers in the US.

Women (aged ≥ 16 years in UK, ≥ 17 years in Northern Ireland and ≥ 18 years in US), with regular menstrual cycles, who presented for EC at a participating study site within 120 hours after UPI and who met the inclusion/exclusion criteria were enrolled into the study. Women presenting more than 72 hours after UPI were eligible for inclusion only if they declined or had contraindications to an IUD insertion.

Significant inclusion criteria included healthy females of the appropriate age for each country, with regular menstrual cycles 24 – 35 (±5) days in length, requesting EC within 120 hours after UPI, who

- Declined insertion of IUD for EC or had a contraindication to an IUD if presenting > 72 hours after UPI,
- Had no current use of hormonal contraception,
- Were willing not to use hormonal contraception until study completion,
- Agreed to use barrier methods of contraception from enrollment to study completion.

Significant exclusion criteria included one or more acts of UPI more than 120 hours before requesting EC, current use of hormonal contraception, pregnancy, breastfeeding, current IUD use, tubal ligation or a partner with a vasectomy, and uncertainty about recent menstrual history.

Subjects were randomized either to UA 30 mg or LNG 1.5 mg in a 1:1 manner. Drug treatment was administered orally according to a randomized procedure generated electronically. Enrollment was to be stopped once study completion was achieved for 827 subjects in each of the two treatment groups who (1) took study drug within 72 hours after UPI and (2) met the criteria for the primary efficacy population. To achieve this sample size objective, the Applicant estimated that overall a total of 2,044 subjects would be enrolled into the study.

The study schedule and conduct were almost identical to that Trial HRA 2914-509 except that blood samples for laboratory safety assessments were not obtained and subjects were assigned to one of two treatment groups instead of a single treatment group.

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.

Similar to Trial 2914-509, am independent DSMB monitored the pregnancies to assess whether each pregnancy was “compatible” or “not compatible” with treatment failure.

Medical Reviewer's Comment

- *A summary of the protocol for this trial can be found in Appendix 2.*

Primary Efficacy Measurements and Analysis

The primary efficacy endpoint was the pregnancy rate, defined as the number of pregnancies occurring after taking EC divided by the number of subjects who took EC.

The primary efficacy analysis compared the upper bound of the 95% CI of the point estimate of the observed pregnancy rate in subjects who took ulipristal within 72 hours after UPI to the estimated expected pregnancy rate in the absence of EC. The estimated expected pregnancy rate was calculated according to the method of Trussell as described previously. Pregnancy status also was assessed as described previously.

The observed pregnancy rate was to be declared statistically significantly lower than the estimated expected pregnancy rate if the upper bound of the 95% CI of the observed pregnancy rate was below the estimated expected pregnancy rate.

Main Secondary Efficacy Analysis

The main secondary efficacy analysis was the determination that the observed pregnancy rate in subjects treated with UA within 72 hours after EC was lower than the Applicant's clinical relevance threshold of a 4% pregnancy rate. UA was to be declared non-inferior to this clinical threshold if the upper limit of the 2-sided 95% CI around the observed pregnancy rate was lower than 4%.

Medical Reviewer's Comment

- *The Applicant's statistical analysis plan stipulated that both the primary and main secondary efficacy analyses needed to be positive for the study to be considered a success.*

Additional Secondary Efficacy Analyses

1. Pregnancy rate within 120 hours of UPI: This analysis compared the upper bound of the 95% CI around the point estimate of the observed pregnancy rate in subjects who took ulipristal within 120 hours after UPI to the estimated expected pregnancy rate in the absence of EC.
2. Prevented fraction of pregnancies: The prevented fraction of pregnancies was calculated in the same manner as in Study HRA 2914-509.
3. Trend in pregnancy rates over time: Pregnancy rates, based on the actual time between UPI and the subject's taking ulipristal, were calculated for each 24-hour period over the interval ranging from 0 to 120 hours.
4. Non-inferiority to LNG: Non-inferiority of ulipristal to LNG would be concluded if the upper bound of the 95% CI around the odds ratio of pregnancy in the ulipristal group relative to the LNG group was lower than the Applicant's prespecified non-inferiority margin of 1.6. Superiority to LNG would be established if the upper bound of the 95% CI around the odds ratio was below 1.0.

Analysis Populations
The analysis populations (ITT, ITT Completers, mITT, mITT2, and PP) were defined according to the same criteria as in Trial HRA 2914-509.

An additional analysis population was:

- Modified Intent-to-Treat Interim Population (interim mITT) was defined as the first 1,200 subjects in the mITT population who enrolled within 72 hours after UPI. The protocol specified an interim analysis at this level of enrollment.

Efficacy analyses that were performed by the Applicant included those using the interim mITT, mITT, mITT2, ITT, ITT Completers, and PP populations. The Applicant considered the mITT population as the primary analysis population.

Medical Reviewer's Comment

- *As described previously for Study HRA 2914-509, the Division also considered the Applicant's mITT population to be the primary efficacy analysis population. However, the Division independently reviewed all pregnancies classified by the DSMB as "not compatible" with an EC failure.*

Interim and Final Analysis
A pre-specified interim analysis was to be performed on the first 1,200 mITT subjects who took EC within 72 hours of UPI. In the event that (1) the upper limit of the 95% CI around the observed pregnancy rate for ulipristal in the mITT population was below the estimated expected pregnancy rate and below the clinical relevance threshold of 4% and (2) ulipristal was determined to be non-inferior to LNG (i.e., the upper bound of the 2-sided 95% CI around the odds ratio of pregnancy rates in the ulipristal group relative to the LNG group was < 1.6), the study would be considered a success and recruitment would be stopped. Otherwise, recruitment would continue as planned until the final sample size was reached.

The interim analyses were considered by the Applicant to represent the primary analysis in support of the efficacy of UA in Study HRA 2914-513.

Medical Reviewer's Comments

- *The Division concurs with the Applicant's decision that the efficacy analyses based on the interim database would be the "primary" analyses in support of the efficacy of UA in Study HRA 2914-513.*
- *At the time of the interim analysis, the planned sample size was close to completion, so that the efficacy analyses of the entire mITT population were also completed and were presented as secondary analyses. The primary efficacy results, however, are the interim efficacy results.*

6 Review of Efficacy

Efficacy Summary

Both phase 3 trials met the protocol-specified criteria for success: upper bound of the 2-sided 95% CI around the observed pregnancy was 1) less than the expected pregnancy rate and 2) less than the clinical relevance threshold of 4%.

This Application demonstrates that a single 30-mg dose of UA 30 mg is effective when used as emergency contraception up to 120 hours after unprotected intercourse. Of particular clinical relevance is the sustained efficacy of ulipristal acetate up to 120 hours of UPI.

6.1 Indication

UA 30 mg tablet is an emergency contraceptive indicated for the prevention of pregnancy following unprotected intercourse or a known or suspected contraceptive failure. The efficacy portion of the Application is supported by two phase 3 clinical trials.

Medical Reviewer's Comment

- *The two phase 2 clinical trials in the application (HRA 2914-507 and HRA 2914-508) did not utilize the UA 30 mg doses proposed for the EC indication. Both phase 3 trials used the to-be-marketed formulation.*

6.1.1 Methods

The basis of FDA approval for products indicated for EC has historically relied on several measures of pregnancy prevention. These measures include (1) the fraction of expected pregnancies that are prevented following use of EC (prevented fraction) and (2) the observed pregnancy rate, compared to the pregnancy rate that would be expected in the study population in the absence of EC.

6.1.2 Demographics

Trial 2914-509
The mean (±SD) age of the 1,533 subjects in the ITT population was 24.4 ± 6.1 years. Most subjects were in the 18 to 25 years age group (69%); approximately 94% of subjects were between the ages of 18 and 35 years. A majority of subjects were White (60.3%), with African American women constituting the second largest group (21.5%). The mean body mass index (BMI) was 25.3 kg/m^2.

The average menstrual cycle length was 29.0 days (range 24 – 35 days), with a majority of subjects (96%) reporting regular menstrual cycles in the previous year. The primary method of contraception was condoms (71.7%), with approximately half of subjects

having used EC previously (52.5%). One half of study subjects had been pregnant in the past and about one third of subjects previously had a live birth.

Trial 2914-513

The two treatment groups were similar with regard to demographics, gynecological history, coital history, and other baseline characteristics. Subject demographics were comparable for both treatment groups with respect to age, distribution of race, and BMI.

Table 4 summarizes subject demographics for the ITT population for both drugs. Mean age was approximately 25 years, with about 4% of the ITT population being < 18 years old and 7% being > 35 years of age. A majority of participants were White (~ 73%), with the second largest group being African American (~19%). The mean BMI was approximately 25 kg/m^2.

Subject demographics for both clinical trials are summarized below.

Table 4 Demographics: Trials 2914-509 and 2914-513

Variables	HRA 2914-509 ITT Population (N=1,533)	HRA 2914-513 ITT Population N=2,221)	
		Ulipristal Acetate n=1,104	Levonorgestrel n=1,117
Age (Years)	24.4 ± 6.1 Median Age 23 Min-Max=18-50	24.5 ± 6.1 Median Age: 23 Min-Max: 16-52	24.9 ± 6.5 Median Age: 23. Min-Max: 16-55
Age Category			
16-17	0%	4.0	4.4
18-35	93.5%	89.5	88.2
36 and older	6.5%	6.5	7.4
Race			
White	60.3%	72.8	72.4
African American	21.5%	19.0	18.5
Asian	2.3%	1.2	1.9
Other	13.9%	7.0	7..2
Body Mass Index (kg/m^2)	25.3 ± 6.2 Median BMI=23.5 Min-Max=16.1-61.3	25.3 ± 5.9 Median BMI: 23.8 Min-Max: 15.8-70.0	25.2±5.7 Median BMI: 23.7 Min-Max: 14.9-53.7
Smoking Status			
Current smoker	32.2%	36.1	31.7
Former smoker	18.9%	12.9	11.7
Never smoked	49.1%	51.0	56.6
Average Menstrual Cycle Length (days)	29.0 (range 24-35)	28.7 (range 24-35)	28.8 (range 23-40)
Previous EC use	52.5%	54.9%	55.7%
Previous pregnancy	52.4%	47.3%	47.8%
Previous live birth	33.6%	31.5%	32.8%

Source: Adapted from Clinical Study Report, Table 4, pages 42 and 43 and FDA Statistical Review.

6.1.3 Subject Disposition

Trial 2914-509

Of the 1,623 subjects who were screened for Study 2914-509, 1,533 were treated and included in the ITT population. Of these 1,533 subjects, 292 subjects (19%) were excluded from the mITT population for the following reasons:

- Unknown pregnancy status after enrollment n=106 (6.9%)
- Greater than 35 years of age n=99 (6.5%)
- Repeat enrollment: n=84 (5.5%)
- Pregnancy not attributable to EC n=3 (0.2%)

Therefore, the primary efficacy mITT population (the Applicant's primary efficacy population) consisted of 1,241 subjects.

Among the 1,533 subjects treated with UA, (the ITT population), 171 (11.2%) discontinued the study prematurely. The most common reason for premature discontinuation was loss to follow-up (102 subjects, 6.7%). Subject disposition is summarized in Table 5.

Trial 2914-513

A total of 2,321 subjects were screened, signed the informed consent form, and were enrolled into the study. A total of 2,221 subjects received study drug (the ITT population). Of the 2,221 treated patients, 1,104 received UA and 1,117 received LNG. Of the 1,104 subjects treated with UA, 163 subjects (15%) were excluded from the mITT population for the following reasons:

- Unknown pregnancy status after enrollment n=77 (7.0%)
- Greater than 35 years of age n=69 (6.3%)
- Repeat enrollment: n=14 (1.3%)
- Pregnancy not attributable to EC n=3 (0.3%)

Therefore, in the UA group, the primary efficacy mITT population (the Applicant's primary efficacy population) consisted of 941 subjects.

Of the 1,117 subjects treated with LNG, 159 subjects (14.2%) were excluded from the mITT population for the following reasons:

- Unknown pregnancy status after enrollment n=57 (5.1%)
- Greater than 35 years of age n=76 (6.8%)
- Repeat enrollment: n=22 (1.9%)
- Pregnancy not attributable to EC n=4 (0.4%)

In the LNG group, the Applicant's primary efficacy population consisted of 958 subjects.

Among the treated subjects, 10 treated with UA and 14 treated with LNG were not eligible for enrollment. Among the 1,104 ulipristal-treated subjects, 1,013 (91.8%) completed all scheduled study visits. The main reason for discontinuation was loss to follow-up in 48 subjects (4.3% of treated subjects). Among the 1,117 LNG-treated subjects, 1,046 (93.6%) completed all scheduled study visits. Of the 71 (6.4%) treated subjects who discontinued the study, 40 (3.6%) were lost to follow-up.

Subject disposition for both clinical trials are summarized in Table 5 below.

Table 5 Subject Disposition: Trials 2914-509 and 2914-513

	HRA 2914-509	HRA 2914-513	
	Ulipristal acetate n	Ulipristal acetate n	Levonorgestrel n
Screened	1,623	2,321	
Treated (ITT population))	1,533	1,104	1,117
Not Eligible but Treated	26	10	14
Completed the Study	1,362 (88.8%)	1,013 (91.8%)	1,046 (93.6%)
Discontinued the Study	171 (11.2%)	91 (8.2%)	71 (6.4%)
Reason for Discontinued			
Lost to follow-up	102 (6.7%)	5 (0.5%)	40 (3.6%)
Other	68 (4.4%)	36 (3.3%)	30 (2.7%)
Withdrew consent	1 (0.1%)	2 (0.2%)	1 (0.1%)
Adverse event	0 (0.0%)	2 (0.2%)	0 (0.0%)

Source: FDA Statistical Review by Kate Dwyer, Ph.D.

6.1.4 Analysis of Primary Endpoint(s)

6.1.4.1 Trial HRA 2914-509

A total of 29 pregnancies were detected at follow-up in women enrolled in this study. The Applicant excluded three pregnancies from the primary efficacy analysis population (mITT) because the DSMB determined that they were not compatible with EC failure (i.e., one pretreatment and two post-treatment pregnancies).

The results of the primary efficacy analysis based on the Applicant's mITT2 and mITT populations and the FDA efficacy population are shown in Table 6.

The Applicant's primary efficacy analysis population (the mITT population) comprised 1,241 women with 26 pregnancies, for an overall pregnancy rate of 2.10% (95% CI: 1.41, 3.10). The observed pregnancy rate in the mITT population (2.10%) was statistically significantly lower than the estimated expected rate of 5.53%, which is based on 69 expected pregnancies if subjects had not used EC. The upper limit of the two-sided 95% CI of the observed pregnancy rate was also lower than the clinical relevance threshold (4%) that is considered clinically meaningful for an EC method.

The Applicant's mITT2 population comprised 1,244 women and included all pregnancies (n=3) considered "not compatible" with an EC failure (and which had been excluded from the mITT population). A total of 29 conceptions occurred in this group

(69 were expected to occur) giving an observed pregnancy rate of 2.33% (95% CI: 1.60, 3.37).

The FDA's primary efficacy population comprised 1,242 women with 27 pregnancies, for an **overall pregnancy rate of 2.17%** (95% CI 1.47, 3.19). The upper limit of the two-sided 95% CI of the observed pregnancy rate (3.19) was statistically significantly lower than the expected pregnancy rate 5.53. The upper limit of the two-sided 95% CI of the observed pregnancy rate was also lower than the clinical relevance threshold (4%).

Table 6 Pregnancy Rates following Ulipristal Treatment Between 48-120 Hours after UPI (Study HRA 2914-509, mITT2, mITT, and FDA Efficacy Populations)

	Applicant's mITT Population N=1,241	**Applicant's mITT2 Population N=1,244**	**FDA Efficacy Population N=1,242**
Estimated Expected Pregnancies per Trussell (n)	69	69	69
Estimated Expected Pregnancy Rate (%)	5.53	5.54	5.53
Observed Pregnancies (n)	26	29	27
Observed Pregnancy Rate (%) (95% CI)	**2.10 (1.41, 3.10)**	**2.33 (1.60, 3.37)**	**2.17 (1.47, 3.19)**

Source: Adapted from Clinical Study Report, Tables 7 and 8, pg. 41 - 42 and FDA Statistical Review

Medical Reviewer's Comments

- *The DSMB determined that two posttreatment pregnancies and one pretreatment pregnancy were "not compatible" with EC failure.*
- *The Division concluded that EC failure could not be completely ruled out in Subject 7/078, whom the DSMB excluded as a pre-treatment pregnancy.*
- *The Division agreed that the two posttreatment pregnancies were likely attributable to an act of intercourse that occurred after EC treatment. Therefore, FDA's primary efficacy population consists of 27 pregnancies in 1,242 subjects, which resulted in a pregnancy rate of 2.17% (95% CI: 1.47, 3.19).*

- *In both the Applicant's primary efficacy analysis and the FDA's efficacy analysis, the observed pregnancy rate in subjects treated with ulipristal 48-120 hours after UPI was shown to be statistically significantly lower than the estimated expected pregnancy rate.*

The three pregnancies deemed non-compatible with EC failure by the DSMB are listed in Table 7 below.

Table 7 Study HRA 2914-509 Non-Compatible Pregnancies per DSMB

Site/Subject	Treatment Visit 1	Follow-up Visit 2	Follow-up Visit 3	Additional Visits	DSMB Conclusion	FDA Conclusion
1/013	2/12/07 LMP: 2/8 Coitus: 2/10 FW*: 2/10-2/16 **Treatment 2/12** +61 hrs. bHCG=1	3/15 HSUP: neg	3/20 HSUP: neg	3/26 Beta: 991 TVU: ?CRL 4/11 TVU: CR: 2mm 47d **Conception: 3/8** Elective abortion on 4/23	Excluded – Post-dose conception	Excluded- Post-dose conception
7/078	11/9/07 LMP: 10/15 Coitus: 11/6 FW*: 11/6-11/12 **Treatment 11/9** +70 hrs. bHCG=6	11/20 bHCG=485 Additional acts of Coitus: 11/11,12,13,15,16	11/21 TVU: 44d ?CRL, no yolk sac **Conception: 10/22**	11/26 Spontaneous Abortion	Excluded – Pre-dose conception	Included- Unable to rule out EC failure
9/041	6/16/07 LMP: 6/1 Coitus: 6/11, 6/13 FW*: 6/11-6/19 **Treatment 6/16** +116 hrs. bHCG=2	7/19 HSUP: Pos. bHCG=602	7/24 TVU: 30d by GS ?CRL **Conception: 7/3**	Pregnancy On-going at data base lock	Excluded – Post-dose conception	Excluded- Post-dose conception

*Fertilization Window = UPI + 6 days

Medical Reviewer's Comment

- *Subject 7/078: No sonographic crown-rump length was seen on 11/21 at supposedly 44 days post conception; therefore, the TVU was not consistent with the dating. No follow-up TVU was performed for this subject. Although she had an abnormal pregnancy, if she conceived on 10/22, as the DSMB calculated, her beta on 11/19 should have been higher than 6. Therefore, we believed the evidence was insufficient to exclude this pregnancy as non-compatible with EC failure.*

A comparison of expected versus observed numbers of pregnancies indicates that UA statistically significantly decreased the number of observed pregnancies relative to the 69 expected pregnancies. The calculation of the estimated number of pregnancies based on cycle day relative to ovulation is shown in Table 8. The number of expected pregnancies for each day is then compared to the observed pregnancies for that day.

Table 8 Expected and Observed Pregnancies Based on Cycle Day, Applicant's mITT Population (Study HRA 2914-509)

Cycle Day of Intercourse	Conception Probability (%)[1]	Number of Subjects (N=1,241)	Number of Expected Pregnancies (N=69)	Number of Observed Pregnancies (N=26)
< -5	0	240	0.0	6
-5	3.6	53	1.9	0
-4	13.6	56	7.6	2
-3	15.5	64	9.9	1
-2	27.7	65	18.0	1
-1	29.8	70	20.9	2
Day of Ovulation	12.3	66	8.1	2
+1	4.5	50	2.3	4
> +1	0	577	0.0	8

Source: Clinical Study Report, Table 8, Page 41

Medical Reviewer's Comment

- *It is interesting to note that 14 of the 26 pregnancies reported in the Applicant's mITT population occurred in women with an assigned conception probability of zero and therefore outside the presumed "fertile window." This may indicate that the expected pregnancy rate may be underestimated in this study so that the actual prevented fraction may be higher than the calculated 62%.*

6.1.4.2 Trial HRA 2914-513

The primary endpoint for this trial was the pregnancy rate after UA treatment 0-72 hours after UPI. The time interval of 0-72 hours was selected as the primary time interval

because the comparator arm, LNG 1.5 mg, was approved as EC for 0-72 hours after UPI. The protocol stipulated that both the primary and main secondary efficacy analyses performed on women taking UA within 72 hours of unprotected intercourse must be positive for the study to be considered a success.

Primary Efficacy Endpoint Analysis - Interim Analysis

A pre-specified interim efficacy analysis was performed on the mITT Interim population composed of the first 1,200 mITT (596 UA-treated subjects and 604 LNG- treated subjects) who took study drug with 72 hours of UPI. There were 9 UA pregnancies and 17 LNG pregnancies in this cohort. None of these pregnancies were considered non-compatible with EC failure by the DSMB so that all were used in the pregnancy rate calculations.

Medical Reviewer's Comment

- *The DSMB concluded that none of the observed pregnancies in either the UA or LNG groups in the interim mITT population was "not compatible" with an EC treatment failure and therefore, all observed pregnancies were included in the interim mITT population. Thus, the Applicant's interim mITT and the interim FDA efficacy populations are identical.*

If the interim analyses met three criteria for success, enrollment into the clinical trial was to be terminated. Otherwise, recruitment would continue as planned until the final sample size was reached. Criteria for success were:

- The upper limit of the 95% CI around the observed pregnancy rate for UA in the mITT population was below the estimated expected pregnancy rate
- The upper limit of the 95% CI around the observed pregnancy rate for UA in the mITT population was below the clinical relevance threshold of 4%
- UA was determined to be non-inferior to LNG (i.e., the upper bound of the 2-sided 95% CI around the odds ratio of pregnancy rates in the UA group relative to the LNG group was < 1.6)

Should the interim analysis be successful, per the Applicant's Statistical Analysis Plan, the primary efficacy analyses and primary efficacy outcomes would be based on the "interim" analyses using the Applicant's interim mITT population. However, by the time the interim analysis was performed, the study had accrued the total sample size. Efficacy analyses were also performed on the entire study population (the mITT population), but as all interim analyses were conclusive, the additional analyses were considered as supportive findings.

The results of the primary efficacy analysis based on the interim mITT population are presented in Table 9. There were 9 pregnancies among 596 subjects in the ulipristal group, resulting in an **observed pregnancy rate of 1.51%** (95% CI: 0.62%, 3.32%). There were 17 pregnancies among 604 subjects in the LNG group, resulting in an

observed pregnancy rate of 2.81% (95% CI: 1.54%, 4.97%). All pregnancies that occurred in the mITT interim analysis population were deemed by the DSMB to be compatible with EC failure. The observed pregnancy rate in each treatment group was statistically significantly lower than the estimated expected pregnancy rate in the respective treatment group (ulipristal: 5.63%, LNG: 5.88%).

Table 9 Pregnancy Rates 0-72 hours of UPI, HRA 2914-513, mITT Interim Population

	Ulipristal acetate (n=596)	**Levonorgestrel (n=604)**
Expected pregnancies per Trussell (n)	33	36
Expected pregnancy rate (%)	5.63	5.88
Observed pregnancies (n)	9	17
Observed pregnancy rate (%) (95% CI)	**1.51 (0.62-3.32)**	**2.81 (1.54-4.97)**
Expected vs. observed P-value	<0.001	<0.001

Source: Clinical Study Report, Table 7, pg. 54 and 55, and FDA Statistical Review.

Medical Reviewer's Comment

- *In the UA treatment group, there were 9 confirmed pregnancies in the interim mITT population and the observed pregnancy rate was 1.51% (95% CI; 0.62, 3.32). This rate was statistically significantly lower than both the expected pregnancy rate of 5.63% and the clinical relevance threshold of 4%. Therefore, the interim efficacy analyses performed for UA in this trial provided good evidence of efficacy.*

Primary Efficacy Endpoint Analysis - Final Analysis (Supportive)

The DSMB determined that 3 UA subjects and 4 LNG subjects in the final database conceived pregnancies non-compatible with EC failure. See Table 10 below.

Table 10 Trial HRA 2914-513 Non-Compatible Pregnancies per DSMB

Site/Subject	Treatment Visit	Follow-up Visit 1	Additional Follow-up	FDA Conclusion
Ulipristal acetate				
21/108	12/29/08 LMP: 11/28 Coitus: 12/29 FW*:12/29-1/4 **Treatment 12/29** +9 hrs. bHCG=314	1/5/09 bHCG=7022 TVU: 35 days IUP **Conception: 12/15** (Originally assessed by PI as 12/13)	(b) (6) Elective abortion	Excluded- Pre-dose conception
35/005	10/7/08 LMP: 9/21 Coitus: 10/5 FW*:10/5-10/11 **Treatment: 10/7** +63 hrs. bHCG=2	11/3/08 bHCG=1364 **Conception: 10/18** (Originally assessed by PI as 10/5)	(b) (6) TVU: 32 day IUP Elective abortion	Included- Compatible with EC failure
40/078	1/7/09 LMP: 12/15 Coitus: 1/5 FW*:1/5-1/11 **Treatment: 1/7** +56 hrs. bHCG=6	1/21/09 bHCG=11,947 **Conception: 12/28** (Originally assessed by PI as 12/27)	(b) (6) TVU: 48 day IUP CRL=6.2 mm Elective abortion	Excluded- Pre-dose conception
Levonorgestrel				
27/021	9/18/08 LMP: 9/3 Coitus: 9/16 FW*: 9/16-9/21 **Treatment: 9/18** +52 hours. bHCG=2	10/29 bHCG=241 TVU: 27 days **Conception: 10/15**	Elective abortion	Excluded- Post-dose conception
24/018	10/28/08 LMP: 9/30 Coitus: 10/26 FW*: 10/26-11/1 **Treatment: 10/28** +46 hours. bHCG=5	11/7 bHCG=1369 HSUP positive **Conception: 10/13**	(b) (6) TVU: 42 days Elective abortion	Excluded- Pre-dose conception
32/006	9/4/08 LMP: 8/27 Coitus: 8/31 FW*: 8/31-9/6 **Treatment: 9/4** +111 hours.bHCG=2	10/15 bHCG=414 HSUP positive TVU: 27 days **Conception: 9/28**	(b) (6) TVU: 43 days CRL=0.2 mm Elective abortion	Excluded- Post-dose conception
38/033	10/13/08 LMP: 9/23 Coitus: 10/11 FW*: 10/11-10/17 **Treatment: 10/13** +38 hs.bHCG=8722	10/27 HSUP positive No TVU No post dose bHCG	Pregnancy status unknown	Excluded- Pre-dose conception

*Fertilization Window = UPI + 6 days

Medical Reviewer's Comments

- *UA Group:*
  - *The Division concluded that Subject 35/005's pregnancy could not be ruled out as an EC failure. At Follow-up Visit 1 on 11/3/08, this subject reported only one act of intercourse post-treatment. This was on 10/12/08 and a condom was used. No other act of coitus was reported since the treatment intake. The subject did not report intercourse on or around 10/18, which was the date of conception determined by the DSMB. Therefore, this pregnancy may have been compatible with an EC failure.*
  - *Subjects 21/108 and 40/078 conceived prior to treatment and therefore were also excluded by the Division.*
- *LNG Group:*
  - *In the LNG group, subjects 27/021 and 32/006 both conceived after their fertile windows, so these pregnancies were not compatible with an EC failure. These subjects were included in the mITT2 cohort but not in the mITT cohort.*
  - *Subject 24/018 and Subject 38/033 both conceived prior to treatment and were not included in either the mITT2 or mITT cohort.*
  - *The Division concurred with the DSMB that pregnancies in the LNG group were not compatible with EC failure.*
- *The Final FDA efficacy population consists of:*
  - *ulipristal: 0-72 hours, (844 subjects, 16 pregnancies)*
    0-120 hours, (940 subjects, 16 pregnancies)
  - *LNG: 0-72 hours, (851 subjects, 22 pregnancies)*
    0-120 hours, (954 subjects, 25 pregnancies)

The final database for the 0-72 hour treatment window included 16 and 22 pregnancies in subjects ≤ 35 years of age (Final FDA efficacy population) in the UA (N=844) and LNG (N=851) treatment groups, respectively (see Table 11). The observed pregnancy rates were 1.90% (CI: 1.13%, 3.12%) and 2.59% (CI: 1.68%, 3.94%) in the ulipristal and LNG treatment groups, respectively. The observed pregnancy rate in each treatment group was statistically significantly lower than the estimated expected pregnancy rate in the respective treatment group (UA: 5.55%, LNG: 5.43%).

The pregnancy rates for both treatments administered 0-72 hours are presented in Table 11.

Table 11 Pregnancy Rates Within 72 hours of UPI, FDA Population, HRA 2914-513

	Ulipristal acetate (n=844)	Levonorgestrel (n=851)
Expected Pregnancies per Trussell (n)	47	46
Expected pregnancy rate (%)	5.55	5.43
Observed pregnancies (n)	16	22
Observed pregnancy rate (%) (95% CI)	**1.90 (1.13, 3.12)**	**2.59 (1.68-3.94)**

Source: FDA Statistical Review

Medical Reviewer's Comment

- *The 16 UA treatment failures that occurred during this trial all occurred during the 0-72 hour time period between UPI and treatment. No pregnancies occurred when UA was administered between 73-120 hours after UPI.*

6.1.5 Analysis of Secondary Efficacy Endpoints

6.1.5.1 Trial HRA 2914-509

Main Secondary Efficacy Analysis - Non-inferiority to the clinical relevance threshold of 4%

The main secondary efficacy analysis was to demonstrate that the pregnancy rate observed after taking UA 30 mg between 48 and 120 hours after UPI was statistically significantly lower than 4% clinical relevance threshold.

As shown in Table 6, the upper bounds of the 95% CIs for the observed pregnancy rates (3.10% [mITT population] and 3.19% [FDA efficacy population]) in the ulipristal-treated subjects were less than 4%, thereby demonstrating non-inferiority to the Applicant's clinical relevance threshold.

Medical Reviewer's Comments

- *The findings from Study HRA 2914-509 support the efficacy of UA in reducing the risk of pregnancy when taken within 48-120 hours after UPI. Both the primary efficacy endpoint (a statistically significant reduction in the observed pregnancy rate compared to the estimated expected pregnancy rate) and the main secondary endpoint (non-inferiority to the clinical relevance threshold of 4%) were achieved. Thus, the trial met the protocol definition of study success.*
- *Although the majority of women enrolled in this study presented for EC after UPI at or near midcycle (days 11–16), a large proportion of women were enrolled after UPI that took place outside their presumed fertile window as defined by the*

conception probabilities model of Trussell et al. This may explain why the estimated expected pregnancy rate in this study (5.5%) is notably lower than that in previous large EC trials (8%).

- *A total of 14 of the 27 observed pregnancies occurred in women whose UPI took place outside their presumed fertile window (day -5 to day +1 relative to anticipated ovulation) and who were, therefore, according to the method of Trussell, assigned a conception probability of zero. This suggests that UPI outside of the supposed midcycle fertile period may indeed result in pregnancy and supports current practice guidelines recommending that EC be administered regardless of cycle day of UPI.*

Other Secondary Analyses

Secondary Efficacy Analyses - Prevented Fraction of Expected Pregnancies

The proportions of pregnancies prevented by treatment with ulipristal 48-120 hours after UPI based on the Applicant's mITT2 and mITT populations and the FDA efficacy populations are presented in Table 12. The prevented fraction of expected pregnancies ranged from 58.0% to 62.3%.

Table 12 Prevented Fraction of Expected Pregnancies, Study HRA 2914-509

Population	Subjects At Risk (n)	Observed Pregnancies (n)	Expected Pregnancies (n)	Prevented Fraction of Expected Pregnancies (%, 95% CI)
Applicant's mITT2	1,244	29	69	58.0 (36.4, 72.0)
Applicant's mITT	1,241	26	69	62.3 (41.9, 75.6)
FDA Efficacy Population	1,242	27	69	60.9 (40.1, 74.5)

Source: Adapted from Clinical Study Report, Tables 12.1 and 12.2, pg. 427-428, and FDA Statistical Review.

Medical Reviewer's Comment

- *A total of 14 of the 27 observed pregnancies in this clinical trial occurred in women whose UPI took place outside their presumed fertile window (day -5 to day +1 relative to anticipated ovulation). Based on these data, the expected pregnancy rate might be an underestimation and, consequently, the actual prevented fraction might be higher than the 62% calculated.*

Secondary Efficacy Analyses - Trend in Pregnancy Rates over Time

Observed and estimated expected pregnancy rates in the FDA efficacy population for the three 24-hour intervals between 48 to 120 hours from UPI to treatment with ulipristal are summarized in Table 13. The observed pregnancy rates were 2.45%, 2.05%, and 1.27% in the intervals of 48-72 hours, 73-96 hours, and 97-120 hour, respectively.

Table 13 Pregnancy Rates by 24-hour Intervals, HRA 2914-509, FDA Efficacy Population

Time from UPI (hours)	Subjects Exposed (n)	Observed Pregnancies (n)	Observed Pregnancy Rate (%) (95% CI)	Expected Pregnancies (n)	Expected Pregnancy Rate (%)
48-72	694	17	2.45 (1.49, 3.96)	42	6.00
73-96	390	8	2.05 (0.95, 4.14)	19	4.95
97-120	158	2	1.27 (0.02, 4.94)	8	4.90
48-120	**1,242**	**27**	**2.17 (1.47, 3.19)**	**69**	**5.53**

Source: FDA Statistical Review

Medical Reviewer's Comments

- *Based on the point estimates of the observed pregnancies rates, there did not appear to be a decrease in efficacy with increasing time from UPI to treatment through 120 hours after UPI.*
- *The upper bounds of the 95% CIs around the observed pregnancy rates were lower than the estimated expected pregnancy rates except for the interval 97-120 hours. The sample size in this latter interval, however, was smaller than that of the other intervals; the study was not powered to evaluate pregnancy rates in individual 24 hour intervals.*
- *Trial HRA 2914-509 demonstrated that the use of UA between 48 and 120 hours after UPI is an effective method of emergency contraception and that the efficacy is sustained up to 120 hours.*

6.1.5.2 Trial HRA 2914-513

Main Secondary Efficacy Analyses - Non-inferiority to the clinical relevance threshold of 4%

As shown in Table 9 for the Interim Analysis, the upper bound of the 95% CI for the observed pregnancy rate in the ulipristal treatment group (3.32%) was less than 4%, thereby demonstrating non-inferiority to the Applicant's clinical relevance threshold. The upper bound of the 95% CI for the observed pregnancy rate in the LNG treatment group (4.97%), however, was greater than 4%.

Medical Reviewer's Comments

- *The findings from Study HRA 2914-513 support the efficacy of UA in reducing the risk of pregnancy when taken within 0-72 hours after UPI. Both the primary efficacy endpoint (a statistically significant reduction in the observed pregnancy*

rate compared the estimated expected pregnancy rate) and the main secondary endpoint (non-inferiority to the clinical relevance threshold of 4%) were achieved in the ulipristal treatment group.

- *The final (or complete) study findings also support the efficacy of UA in reducing the risk of pregnancy when taken within 0-72 hours after UPI. Both the primary efficacy endpoint (a statistically significant reduction in the observed pregnancy rate compared to the estimated expected pregnancy rate) and the main secondary endpoint (non-inferiority to the clinical relevance threshold of 4%) were achieved in the ulipristal treatment group, based on the final database.*

Secondary Efficacy Analyses - Non-inferiority of Ulipristal to LNG

For the interim mITT population, UA was non-inferior to LNG when taken within 72 hours of UPI (odds ratio for pregnancy: 0.53), as the upper bound of the 95% CI of the odds ratio (1.44) was lower than the protocol-defined non-inferiority margin of 1.6 (see Table 14). Superiority, however, was not established because the upper bound of the 95% CI of the odds ratio crossed 1.0, the protocol-defined criterion for superiority.

Table 14 Odds Ratio (95%) of Pregnancy Rate of Ulipristal Relative to Levonorgestrel Administered within 72 hours of UPI (HRA 2914-513, Interim mITT)

	Ulipristal acetate N=596	**Levonorgestrel N=604**
Observed Pregnancy (n)	9	9
Observed Pregnancy Rate (%)	1.51	2.81
Odds Ratio (95% CI)	**0.53 (0.20, 1.44)**	

Source: Clinical Study Report, Table 9.1.1, pg. 443.

Secondary Efficacy Analyses - Prevented Fraction of Pregnancies

The prevented fraction of pregnancies in the Final FDA efficacy population was 66.0% (95% CI: 42.5 to 79.9%) when UA was taken within 0-72 hours after UPI and 70.4% (95% CI: 49.9 to 82.5%) when ulipristal was taken within 0-120 hours after UPI. See Table 15.

Table 15 Prevented Fractions, HRA 2914-513, FDA Population

Time interval between EC treatment and UPI	**Ulipristal Acetate % (95%CI)**	**Levonorgestrel % (95% CI**
0-72 hrs	66.0 (42.5, 79.9)	52.2 (25.1, 69.5)
0-120 hrs	70.4 (49.9, 82.5)	52.8 (27.8, 69.2)

Source: FDA Statistical Review

Secondary Efficacy Analyses - Trend in Pregnancy Rates over Time

Observed pregnancy rates in the Final FDA efficacy population for the five 24-hour intervals between 0 to 120 hours from UPI to treatment with UA or LNG are summarized in Table 16. The observed pregnancy rates in the UA group were 1.60%, 2.13%, and 1.96%, respectively, at 0-24, 25-48, and 49-72 hour intervals. No pregnancies were observed in the ulipristal group in the 73-96 and 97-120 hour intervals.

Table 16 Pregnancy Rates by 24-Hour Time Interval, HRA 2914-513, FDA Population

	Ulipristal acetate			Levonorgestrel		
Time from UPI (hours)	**Exposed Subjects (n)**	**Observed Pregnancies (n)**	**Observed Pregnancy Rate (%) (95% CI)**	**Exposed Subjects (n)**	**Observed Pregnancies (n)**	**Observed Pregnancy Rate (%) (95% CI)**
0-24	312	5	1.60 (0.56, 3.88)	337	10	2.97 (1.52, 5.52)
25-48	329	7	2.13 (0.92, 4.49)	319	7	2.19 (0.95, 4.63)
49-72	204	4	1.96 (0.56, 5.22)	196	5	2.55 (0.90, 6.11)
73-96	63	0	0.0 (-, -)	73	2	2.74 (0.13, 10.3)
97-120	32	0	0.0 (-, -)	29	1	3.45 (-0.93, 19.17)
0-120	**940**	**16**	**1.70 (1.01, 2.80)**	**954**	**25**	**2.62 (1.75, 3.89)**

Source: FDA Statistical Review

As shown in Table 16 above, in the UA treatment group, the observed pregnancy rate within 120 hours of UPI for the FDA efficacy population (N = 940) was 1.70% (95% CI; (1.01, 2.80). In the LNG treatment group, the observed pregnancy rate from 0-120 hours (N = 954) was 2.62% (1.75, 3.89).

Table 17 compares these observed rates to the expected rates for the 0-120 hour treatment window. Both UA and LNG pregnancy rates were statistically significantly lower than the calculated expected pregnancy rate of 5.72% and 5.52%, respectively. Both rates were also lower than the clinical relevance threshold of 4%.

Table 17 Expected and Observed Pregnancy Rates after Ulipristal Treatment within 120 hours of UPI, FDA Population

	Ulipristal acetate N=940	Levonorgestrel N=954
Estimated Expected Pregnancies per Trussell (n)	54	53
Expected pregnancy rate (%)	5.72	5.52
Observed pregnancies (n)	16	25
Observed pregnancy rate (%) (95% CI)	**1.70 (1.01, 2.80)**	**2.62 (1.75, 3.89)**

Source: FDA Statistical Review

Medical Reviewer's Comment

- *The 30 mg dose of UA, whether administered within 72 or 120 hours after unprotected intercourse, statistically significantly lowered the observed pregnancy rate compared to the expected pregnancy rate in the absence of EC.*

6.1.6 Other Endpoints

Logistic regression modeling with the co-variates of age and body mass index (BMI ≤ 30 kg/m^2 or > 30 kg/m^2) indicated a statistically significant impact for BMI on pregnancy rates. As age and BMI may have important implications for the counseling and clinical management of women seeking EC, subgroup analyses of these two variables were explored in detail.

6.1.7 Subpopulations

Effect of Body Mass Index on Efficacy

Observed and estimated expected pregnancy rates by BMI (≤ 30 kg/m^2 or > 30 kg/m^2) are presented for each of the two phase 3 studies as well as for the pooled phase 3 data (see Table 18). In women with BMI > 30 kg/m^2, the upper limits of the 95% CIs were consistently greater than the respective expected pregnancy rate and higher than the clinical relevance threshold of 4% indicating reduced efficacy for both ulipristal and LNG in the heavier subgroup.

For women with a BMI > 30 kg/m^2 who received ulipristal in Trial HRA 2914-509, the upper bound of the 95% CI for the observed pregnancy rate (6.45%) was greater than the estimated expected pregnancy (4.37%). For women with a BMI > 30 kg/m^2 who received ulipristal in Trial HRA 2914-513, the upper bound of the 95% CI for the observed pregnancy rate (9.29%) also was greater than the estimated expected pregnancy (4.61%).

The effect of BMI on the observed pregnancy rate in subjects treated with LNG within 72 hours after UPI appeared to be greater than that in ulipristal-treated subjects. For women with a BMI > 30 kg/m^2 who received LNG within 72 hours after UPI in Trial HRA

2914-513, both the upper bound of the 95% CI for the observed pregnancy rate (13.42%) and the point estimate of the observed pregnancy rate were greater than the estimated expected pregnancy rate of 4.38%.

Table 18 Pregnancy Rates by Body Mass Index, 2914-509 and 2914-513, FDA Population

Study / Time Window	BMI Subgroup (kg/m^2)	Ulipristal acetate			Levonorgestrel		
		Pregnancies / Subjects (n / N)	Observed Pregnancy Rate (%) (95% CI)	Expected Pregnancy Rate (%)	Pregnancies/ Subjects (n / N)	Observed Pregnancy Rate (%) (95% CI)	Expected Pregnancy Rate (%)
HRA 2914-509	**BMI ≤ 30**	21 / 1,035	2.03 (1.30, 3.13)	5.76	NA		
48 – 120	**BMI > 30**	6 / 207	2.90 (1.15, 6.45)	4.37			
48 – 120 Hour Total		27 / 1,242	2.17 (1.47, 3.19)	5.25			
HRA 2914-513	**BMI ≤ 30**	11 / 717	1.53 (0.81, 2.80)	5.71	12 / 716	1.68 (0.91, 2.98)	5.63
0 – 72	**BMI > 30**	5 / 127	3.94 (1.41, 9.29)	4.61	10 / 135	7.41 (3.86, 13.42)	4.38
0 – 72 Hour Total		16 / 844	1.90 (1.13, 3.12)	5.55	22/ 851	2.59 (1.68, 3.94)	5.43
Pooled	**BMI ≤ 30**	32 / 1,832	1.75 (1.22, 2.48)	5.83	14 / 800	1.75 (1.00, 2.98)	5.71
0 – 120	**BMI > 30**	11 / 350	3.14 (1.67, 5.68)	4.48	11 / 154	7.14 (3.85, 12.6)	4.53
0 – 120 Hour Total		43 / 2,182	1.97 (1.45, 2.67)	5.45	5.61	2.62 (1.75, 3.89)	5.52

Source: FDA Statistical Review.

Medical Reviewer's Comments

- *The analysis population for Study HRA 2914-509 is the FDA efficacy population.*
- *The analysis population for Study HRA 2914-513 is the Final FDA efficacy population.*
- *The conclusions that can be made regarding the efficacy of ulipristal in women with a BMI > 30 kg/m^2 are somewhat limited by the relatively small sample size (i.e., only approximately 16% of subjects treated with ulipristal had a BMI > 30 kg/m^2). The small sample size likely contributed to the wide 95% CIs.*

Efficacy by Subject Age

Subgroup analysis of pregnancy rates by age group (< 18, 18 to 35, and > 35 years old) for Study HRA 2914-513 individually and pooled with Study HRA 2914-509 are

presented in Table 19 and Table 20, respectively. In the pooled analysis, there was no apparent effect of age on the efficacy of ulipristal, although the results are difficult to interpret due to the small sample sizes in the < 18 and > 35 year subgroups (< 18 years old: N=34; > 35 years old: N=159).

Table 19 Pregnancy Rates by Age, within 72 hours of UPI, HRA 2914-513, FDA Efficacy Population

Age Group	Ulipristal acetate			Levonorgestrel		
	Pregnancies / Subjects (n / N)	Observed Pregnancy Rate (%) (95% CI)	Expected Pregnancy Rate (%)	Pregnancies / Subjects (n / N)	Observed Pregnancy Rate (%) (95% CI)	Expected Pregnancy Rate (%)
< 18	0 / 34	0.0 (-, -)	6.74	1 / 43	2.33 (-0.76, 13.60)	5.41
18 – 35	16 / 810	1.98 (1.18, 3.25)	5.50	21 / 808	2.60 (1.67, 4.00)	5.43
> 35	2 / 64	3.13 (0.17, 11.6)	5.93	1 / 66	1.52 (-0.56, 9.16)	7.73

Source: FDA Statistical Review.

Table 20 Ulipristal Pregnancy Rates by Age Within 120 Hours of UPI (Pooled Phase 3 Studies)

Age Group	Observed Pregnancies (n)	Exposed Subjects (n)	Observed Pregnancy Rate (%) (95% CI)	Expected Pregnancies (n)	Expected Pregnancy Rate (%)	Prevented Fraction (%) (95% CI)
< 18	0	34	0.0 (-, -)	2	6.74	100.0 (100.0, 100.0)
18–35	43	2,148	2.00 (1.47, 2.71)	120	5.59	63.3 (47.5, 74.3)
> 35	2	159	1.26 (0.03, 4.89)	10	6.51	80.0 (22.0, 94.9)
Total	45	2,341	1.92 (1.42, 2.59)	132	5.67	66.2 (51.9, 76.2)

Source: FDA Statistical Review

Medical Reviewer's Comments

- *The analysis population for study HRA 2914-509 is the FDA efficacy population + subjects > 35 years of age.*
- *The analysis population for study HRA, 2914-513 is the Final FDA efficacy population + subjects > 35 years of age.*

Trend in Pregnancy Rates over Time

Observed and estimated expected pregnancy rates were determined for the five 24-hour intervals from 0-120 hours between UPI and UA treatment using pooled data from the two phase 3 studies. The results of the analysis based on the FDA efficacy populations for Trials HRA 2914-509 and HRA 2914-513 (competed study) are shown in Table 21. There were no significant differences in the observed pregnancy rates or prevented fractions of pregnancies across the five time intervals.

Table 21 Trend Analysis of Pregnancy Rates by 24-hour Interval between UPI and Ulipristal (Pooled Phase 3 Studies)

Time from UPI (hours)	Observed Pregnancies (n)	Exposed Subjects (n)	Observed Pregnancy Rate (%) (95% CI)	Expected Pregnancies (n)	Expected Pregnancy Rate (%)	Prevented Fraction (%) (95 CI)
0 - 24	5	312	1.60 (0.56, 3.88)	15	4.73	66.7 (19.2, 86.2)
25 - 48	7	329	2.13 (0.92, 4.49)	19	5.86	63.2 (20.5, 82.9)
49 - 72	21	898	2.34 (1.50, 3.60)	55	6.09	60.4 (36.6, 75.2)
73 - 96	8	453	1.77 (0.82, 3.56)	24	5.30	65.2 (28.3, 83.1)
97 - 120	2	190	1.05 (0.02, 4.12)	10	5.10	77.8 (12.0, 94.4)
0 - 120	43	2,182	1.97 (1.45, 2.67)	122	5.45	63.9 (48.3, 74.7)

Source: FDA Statistical Review

Medical Reviewer's Comment

- *The analysis population for study HRA 2914-509 is the FDA efficacy population and that for Study HRA 2914-513 is the Final FDA efficacy population*
- *Trend analysis of pregnancy rates over time was a secondary endpoint in Trial 2914-513 as shown in Table 16.*

Overall Summary of Efficacy

Both phase 3 studies demonstrated that treatment with UA administered within 120 hours after UPI resulted in an observed pregnancy rate that was (1) statistically lower than the expected pregnancy rate in the absence of EC and (2) lower than the clinical relevance threshold of 4%. Similar efficacy results were observed in the primary analysis using different analysis populations (e.g., mITT, mITT2, FDA efficacy population). Results of secondary efficacy analyses supported the findings of the

primary analyses. No effect of age on the efficacy of ulipristal was observed. The efficacy of ulipristal remained consistent regardless of the time interval between UPI and treatment with ulipristal up to 120 hours after UPI. The effectiveness of ulipristal (as well as LNG for EC), however, appeared to be attenuated in subjects with a BMI > 30 kg/m^2.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

There is only one dosage regimen for this drug product. The medication can be taken within 120 hours after UPI without regard to meals.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Persistence of efficacy and/or tolerance effects was not discussed in the submission. No persistent effects would be expected for this product. Proposed labeling notes that protection against pregnancy does not carry over to subsequent acts of UPI that occur after dosing.

6.1.10 Additional Efficacy Issues/Analyses

No additional efficacy issues/analyses were presented.

7 Review of Safety

Safety Summary

The ulipristal safety database includes data from nine phase 1 PK/PD studies, two phase 2 studies, and two phase 3 studies. (See Table 22.) All studies, with the exception of one phase 1 study, used single doses of UA. Four of the phase 1 studies and both phase 3 studies used the to-be-marketed formulation (30 mg of micronized UA). The studies providing the majority of safety data in this Application are phase 3 studies HRA 2914-509 and HRA 2914-513.

Overall, 4,789 subjects received ulipristal and were studied for safety in the clinical development program. Among the 4,789 subjects, 2,764 (58%) received the to-be-marketed 30 mg ulipristal tablet. Four repeat enrollers were reported in the phase 2 studies. In the phase 3 studies, 88 subjects received ulipristal more than once (76 enrolled twice and 12 others enrolled three times). Safety analyses were performed on the ITT population (all subjects who received treatment with ulipristal).

All pregnancies that began during clinical trials of UA were followed to term to determine outcome (spontaneous or elective termination or birth). Details regarding birth outcome, including presence or absence of any birth defects, congenital malformations, or maternal or newborn complications, were recorded.

The overall subject exposure to UA is shown in Table 22.

Table 22 Overall Exposure-Safety Populations for Ulipristal

Ulipristal Dose	Subjects	Duration
Doses below the to-be-marketed dose	35	84 days
Doses below the to-be-marketed dose	677	Single Dose
Dose equivalent to the to-be-marketed dose (i.e., 50 mg non-micronized)	1,276	Single dose
30 mg micronized tablet (to-be-marketed formulation)	**2,764**	Single dose
Doses 2-4 times the to-be-marketed dose	37	Single dose
All Doses	**4,789**	

Source: Summary of Clinical Safety, Adapted from Table 2.7.4-1, Page 9

7.1 Methods

All adverse events (AEs) were collected by open questioning from the time the subject gave her informed consent to the end of the study. In the two phase 2 studies, subjects were asked to fill in a three-day diary with a yes/no response to a predefined checklist of adverse events including nausea, vomiting, breast tenderness, fatigue, lower abdominal pain, diarrhea, and headache. In the phase 3 studies, subjects were asked to record in a home diary calendar any AEs experienced between treatment and post treatment clinic visits.

All adverse events in the phase 2 and phase 3 trials were coded using the Medical Dictionary for Regulatory Activities (MedDRA). MedDRA is a hierarchical medical coding dictionary in which adverse events are classified and organized as follows:

System Organ Class (SOC)
High Level Group Term (HLGT)
High Level Term (HLT)
Preferred Term (PT)

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Phase 1 Trials
All the 9 phase 1 trials utilized a single dose of UA with the exception of Study HRA 2914-510 in which subjects received daily oral doses of 2.5, 5 or 10 mg of UA or matching placebo for 12 weeks. Three of the 9 phase 1 trials used the to-be-marketed single dose of 30 mg formulation of UA.

HRA 2914-510
This was a multiple dose study enrolling 46 healthy women. Laboratory analyses included liver functions, electrolyte profile, creatinine, blood sugar, cholesterol and triglycerides. Overall, 41 (89%) subjects experienced at least one AE. The most frequently reported AE was headache in all treatment groups. Three SAEs were reported; one woman was diagnosed with Graves' disease four weeks after the end of treatment with 5 mg ulipristal acetate, but TSH and thyroid antibodies were already abnormal at baseline. The second woman experienced acute abdominal pain and fever requiring hospitalization. Laboratory tests were inconclusive but the event was considered unlikely to be related to the study drug. A third woman had a preexisting dermoid ovarian cyst which was removed two years after stopping the study treatment.

Endometrial biopsy was performed after approximately 10 weeks of treatment. No endometrial samples displayed hyperplasia or any atypia.

HRA 2914-511
This was a single dose study using the to-be-marketed 30 mg tablet. The study assessed blood count (CBC), chemistry profile, renal and liver function and lipids (total cholesterol, HDL, LDL, triglycerides) both at screening and at the end of the study. A total of 164 treatment-emergent AEs were experienced by 29 subjects (40% after UA and 60% after placebo). The most frequent suspected treatment-related AE was headache (5.5% in the UA group, 20.7% in the placebo group).

HRA 2914-512
This was a single dose study using the to-be-marketed 30 mg tablet. The study assessed CBC, chemistry profile, renal and liver functions both at screening and at the end of the study. A total of 28 treatment-emergent AEs were experienced by 13 subjects (68.4%). The most frequent suspected treatment-related AEs were nausea, abdominal pain, and headache, with a higher occurrence under fasting conditions.

HRA 2914-516
This was a single dose study using the to-be-marketed 30 mg tablet. CBC, chemistry profile, renal and liver function tests were assessed at screening and at the beginning of period two (before second treatment intake), and at end of the study. A total of seven treatment-emergent AE were experienced by five subjects (9.4%). The most frequent suspected treatment-related AEs were vomiting and nausea.

Phase 2 Trials
No laboratory data were obtained in the phase 2 trials.

Phase 3 Trials
The majority of the safety data included in this submission was obtained from the two primary phase 3 clinical trials.

7.1.2 Categorization of Adverse Events

All AEs, whether serious or not, were collected by open questioning from the time the subject gave her informed consent up to the end of the study. Each AE was evaluated for duration, intensity and association with the study medication and other causes. The action taken and the subject outcome were also recorded. The intensity of the AE was characterized as mild, moderate, or severe. In addition in the two phase 2 studies, subjects were asked to fill in a three-day diary with a yes/no response to a predefined checklist of events including nausea, vomiting, breast tenderness, fatigue, lower abdominal pain, diarrhea and headache. The daily severity of nausea and vomiting were also recorded. In the phase 3 studies, subjects were asked to record any AEs experienced between treatment and follow-up in a home diary calendar.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

No pooling of data for the phase 1 studies was attempted due to the differences in formulations and doses.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Overall, 4,789 subjects were studied for safety in the clinical development program. Among the 4,789 subjects, 2,764 (57.9%) received the to-be-marketed 30 mg UA tablet.

Table 23 Overall Exposure – Safety Populations of Phase 1, 2 and 3 Trials

Study	Treatment dose, route, regimen of Ulipristal Acetate	Subjects evaluated for safety	Study duration
HRA2914-501	-10 mg unmicronized and micronized capsule; -10 mg micronized tablet	10	Single dose
HRA2914-503	-Up to 200 mg	31	Single dose
HRA2914-504	-30 mg micronized tablet	20	Single dose
HRA2914-505	-Up to 100 mg	32	Single dose
HRA2914-506	-Up to 100 mg	41	Single dose
HRA2914-510	-2.5 mg -5 mg -10 mg	12 12 11	84 days
HRA2914-511	-30 mg micronized tablet*	35	Single dose
HRA2914-512	-30 mg micronized tablet*	19	Single dose
HRA2914-516	-30 mg micronized tablet*	53	Single dose
HRA2914-507	-50 mg / Placebo -0.75 mg x 2 LNG	832 840	Two doses 12 hours apart
HRA2914-508	-10 mg micronized -10 mg unmicron. -50 mg unmicron.	399 214 413	Single dose
HRA2914-509	-30 mg micronized*	1,533	Single dose
HRA2914-513	-30 mg micronized*/ -1.5 mg LNG	1,104 1,117	Single dose

Source: Summary of Clinical Safety, Adapted from Table 2.7.4-1, Page 9,
*To-be-marketed dose of UA

7.2.2 Explorations for Dose Response

No explorations of dose response were performed, as only one dose was utilized in the phase 3 trials.

7.2.3 Special Animal and/or In Vitro Testing

See Pharmacology/Toxicology Review.

7.2.4 Routine Clinical Testing

Routine clinical testing was performed in one phase 3 clinical trial (Study HRA 2914-509). A total of 112 subjects had both screening and end-of-study clinical laboratory assessments.

7.2.5 Metabolic, Clearance, and Interaction Workup

See Clinical Pharmacology Review.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Potential safety concerns identified with the use of currently available SPRMs are based primarily on the use of mifepristone used as an abortifacient. Other likely adverse outcomes are related to the demonstrated pharmacologic properties of SPRMs.

Medical Reviewer's Comment

- *Safety concerns regarding off-label use of UA and possible abortifacient activity will be addressed later in this review.*

7.3 Major Safety Results

7.3.1 Deaths

No deaths were reported in the clinical development program.

7.3.2 Nonfatal Serious Adverse Events

Phase 1 Trials:

- Four serious adverse events (SAEs) (bacterial pneumopathy, abdominal pain and fever, Grave's disease, and pilonidal cyst) were reported in the phase 1 clinical studies. None were considered to be treatment-related by the investigators.

Phase 2 Trials:

- Study HRA 2914-507: Two SAEs in UA-treated subjects were reported in this study. One subject had a kidney infection 2 months after UA intake and the second subject had pelvic inflammatory disease approximately 1 month after UA treatment. Neither SAE was considered by the investigators to be treatment-related.
- Study HRA 2914-508: No SAEs were reported.

Phase 3 Trials

Four SAEs were reported.

- Study HRA 2914-509:
  One SAE (Subject 023-070, seizures with ecstasy use) was reported during the study. This was considered by the investigator not to be drug-related.

Medical Reviewer's Comment

- *Subject 23-070: This 21-year-old white/Native American female subject had a history of seizures which began in 2005, at the age of 18. She experienced one*

seizure the week prior to her enrollment in the study. Concomitant medication included Valium, methylenedioxymethamphetamine (ecstasy) and marijuana. She took UA on 11/26/07. On (b) (6)*, she experienced 3 seizures. She was hospitalized the same day. She was discharged from the hospital on* (b) (6)*. The subject was diagnosed with "ecstasy-related seizures as well as a differential diagnosis of ecstasy-related Wolf-Parkinson-White Syndrome." She had a history of ecstasy use with previous seizures. The event was considered as not related to the study drug.*

- Study HRA 2914-513:
  Seven SAEs were reported during the study; 3 in the UA treatment group (urinary tract infection, right contact lens-related corneal ulcer, and dizziness) and 4 in the LNG treatment group (vomiting blood-stained fluid, molar pregnancy, ruptured ovarian cyst, and kidney stones). Of these, only dizziness (UA) and molar pregnancy (LNG) were considered possibly related to the study drug.

7.3.3 Dropouts and/or Discontinuations

Phase 3 Trials

- Study HRA 2914-509: Of the 171 treated subjects in the ITT population who discontinued the study, 102 (59.6%) were lost to follow-up, 68 were discontinued for other reasons (mainly subjects who had at least one negative pregnancy test, but for whom menses had not returned and did not attend further follow-up) and one withdrew consent. No subject was discontinued due to an AE.

- Study HRA 2914-513: Two UA treated subjects discontinued from the study due to an adverse event. One subject vomited within 15 minutes of treatment, which was considered related to treatment. The second subject was found to have an ovarian cyst that burst 15 days after treatment, which, according to the investigator's assessment, did not fulfill seriousness criteria and was not considered treatment-related. She did not return for further follow-up so was considered a discontinuation.

7.3.4 Significant Adverse Events

No additional significant adverse events were reported in the clinical trials.

7.3.5 Submission Specific Primary Safety Concerns

There were no submission-specific primary safety concerns.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Phase 2 Trials

The phase 2 trials did not utilize the to-be-marketed dose of UA. A total of 76.4% of the subjects (2,061/2,698) reported at least one AE (73% in the 10 mg unmicronized group, 79% in the 10 mg micronized group, 77% in the 50 mg unmicronized group and 76% in the LNG group). No AEs leading to discontinuation of the study treatment and no deaths were reported.

Table 24 lists the incidence of adverse events occurring in the phase 2 trials.

Table 24 Incidence of Adverse Events, ITT Population, Phase 2 Trials

	HRA 2914-508			**HRA 2914-507**	**Pooled Studies (507, 508)**	**HRA 2914-507**
	UA 10 mg unmicro. n = 214	UA 50 mg unmicro. n = 413	UA 50 mg unmicro. n = 413	UA 50 mg unmicro. n = 832	UA 50 mg n = 1,245	Levonorgestrel 0.75 mg x 2 n = 840
At least one AE (%)	157 (73)	314 (76)	314 (76)	639 (77)	953 (77)	636 (76)
At least one SAE (%)	0	0	0	2 (0.2)	2 (<1)	0
Most Common AE (%):						
Fatigue	56 (26)	102 (26)	101 (24)	312 (37)	413 (33)	300 (36)
Headache	54 (25)	120 (30)	121 (29)	269 (32)	390 (31)	274 (33)
Nausea	60 (28)	132 (33)	99 (24)	256 (30)	355 (28)	221 (26)
Pelvic / ovarian / uterine pain	70 (32)	135 (33)	138 (33)	160 (19)	298 (23)	167 (19)
Dizziness	30 (14)	65 (16)	57 (13)	165 (19)	222 (17)	147 (18)
Breast tenderness	27 (13)	53 (13)	49 (11)	135 (16)	184 (14)	140 (17)
Diarrhea	15 (7)	48 (12)	40 (9)	105 (12)	145 (11)	101 (12)
Dysmenorrhea	4 (2)	6 (2)	11 (2)	68 (8)	79 (6)	59 (7)

Source: Summary of Clinical Safety, Adapted from Table 2.7.4-4, Page 16

Phase 3 Trials

Study HRA 2914-509

Overall, 876 (61.4%) of the treated subjects experienced a total of 2,232 AEs, of which 49.6% were considered treatment-related. The majority (89.1%) of the AEs were mild

or moderate in intensity and spontaneously resolved. No women were discontinued from the study because of adverse events.

The percentage of women who experienced at least one adverse event was comparable in the safety population (n=1,533) and in the primary efficacy population (n=1,241). Women who enrolled more than one time did not experience adverse events more frequently than women who enrolled only once

The most common AEs related to UA use were headache, nausea, abdominal pain, dysmenorrhea, dizziness and fatigue. The nature and frequency of the most common adverse events reported in this study (headache, nausea, and abdominal pain) mirror those reported in similarly sized studies of approved levonorgestrel emergency contraception products[1].

Study HRA 2914-513

Of the 1,104 UA subjects, 597 (54.1%) experienced 1,506 AEs, of which 675 (44.8%) were considered as possibly treatment-related by the investigator. The most frequently experienced treatment-related AEs were nausea (9.4%), headache (8.4%) and dysmenorrhea (7.0%). The majority of the AEs (93.9%) were mild or moderate in intensity and resolved spontaneously. Only one SAE (dizziness) was considered possibly related to the study drug. Two UA treated subjects were withdrawn due an AE: one case of vomiting (considered treatment related) and one ovarian cyst rupture (not considered related).

Common adverse events considered by the investigators to be drug-related and reported by at least 1% of subjects treated with UA in one or both phase 3 studies are presented in Table 25. The most common drug-related adverse reactions reported by subjects treated with UA were nausea, headache, dysmenorrhea, abdominal pain, fatigue, and dizziness.

[1] von Hertzen H, Piaggio G, Ding J, Chen J, Song S, Bartfai G, et al. Low dose mifepristone and two regimens of levonorgestrel for emergency contraception: a WHO multicentre randomised trial. Lancet 2002; 360:1803–10.

Table 25 Common Drug-Related Adverse Events (≥ 1% of Subjects), ITT

	HRA 2914-509	HRA 2914-513	Pooled Data (509 + 513)	HRA 2914-513
Drug	**Ulipristal acetate (N=1,533) n (%)**	**Ulipristal acetate (N=1,104) n (%)**	**Ulipristal acetate (N=2,637) n (%)**	**Levonorgestrel (N=1,117) n (%)**
Nausea	141 (9)	104 (9)	245 (9)	91 (8)
Headache	143 (9)	93 (8)	236 (9)	84 (8)
Dysmenorrhea	63 (4)	77 (7)	140 (5)	94 (8)
Abdominal pain (unspecified)	104 (6)	34 (3)	138 (5)	50 (5)
Fatigue	52 (3)	40 (3)	92 (4)	29 (3)
Dizziness	53 (3)	34 (3)	87 (3)	34 (3)
Upper abdominal pain	33 (2)	20 (2)	53 (2)	32 (3)
Pelvic pain	34 (2.2)	1 (0.1)	35 (1.3)	2 (0.2)
Back pain	15 (1.0)	14 (1.3)	29 (1.1)	7 (0.6)
Vomiting	15 (1.0)	11 (1.0)	26 (1.0)	4 (0.4)

Source: Summary of Clinical Safety, Adapted from Table 2.7.4-6, Page 20,

Medical Reviewer's Comment

- *The nature and frequency of the most common adverse events in the phase 3 ulipristal treatment groups were similar to those in the LNG treatment group.*

Repeat Enrollers

Repeat enrollments in efficacy trials occurred in 88 women (4 in the phase 2 trials and 84 in phase 3 trials). A total of 84/2637 (3.2%) subjects were enrolled in the phase 3 studies more than once; 75 enrolled twice and 9 enrolled three times. These repeat enrollers did not have an increase in the incidence or severity of AEs, no increase in abnormal laboratory parameters, no differences in the duration or volume of bleeding and no increase in the incidence of intermenstrual bleeding after taking UA.

Ovarian Cysts

Three single-dose phase 1 studies included systematic ultrasonographic evaluation for ovarian cysts (Studies HRA 2914-505, -506, and -511). Ovarian cysts, ranging from 12 to 52 mm, were observed in all treatment groups, including placebo, and did not appear to be dose-related. All cysts resolved spontaneously except for one subject with a persistent 16 mm cyst at 3 months of follow up.

In the phase 2 studies, ovarian cysts were reported in both ulipristal groups (10 mg and 50 mg) with equal frequency.

In phase 3 Study HRA 2914-513, one AE of ovarian cyst rupture was reported in each of the ulipristal and LNG treatment groups.

Menstrual Cycle Changes

Cycle length and bleeding patterns of the treatment cycle were also evaluated. Menstrual calendar data was used to evaluate cycle length and bleeding patterns of the cycle in which study drug was administered. Menstrual cycle length was defined as the number of days from the first day of bleeding up to and including the day before the next menses.

Study HRA 2914-509: Menstrual cycle length increased from a mean of 29.0 days as reported at enrollment to 31.8 days, according to data collected in diaries. The average duration of bleeding was 5.1 days (range 1.0-20.0) for the ITT subjects who reported return of menses. The volume of bleeding was reported as regular in 79.2% of these subjects, heavy in 15.9% and described as spotting in 4.9%. A total of 256 women (19.2%) reported a delay of greater than 7 days in the onset of menses after treatment, and 94 (7%) experienced a delay of 15 days or more.

After treatment, 134 women (8.7%) experienced intermenstrual bleeding, compared to intermenstrual bleeding reported by 51 women (3.3%) before enrollment (based on the 3 months prior to enrollment). A majority of these subjects (92%) described the intermenstrual bleeding as spotting.

Study HRA 2914-513: Date of menses after treatment was available for 1,011 subjects in the ulipristal treatment group and 1,031 in the LNG treatment group. The menstrual cycle length in the treatment cycle averaged 30.8 days for the ulipristal-treated subjects and 27.5 days for the LNG-treated subjects. Treatment with ulipristal was associated with a mean increase of 2.1 days from the historical average length as reported by the subjects. The average duration of bleeding was 5.2 days. The majority of these subjects (64.0%) reported regular menstrual volume, while 33.8% reported menses with heavy bleeding. Post-treatment, 95 (8.6%) subjects experienced inter-menstrual bleeding other than menses, the majority of which was described as spotting.

Medical Reviewer's Comments

- *In Study HRA 2914-513, 33% of the ulipristal treated subjects and 35.5% of the levonorgestrel subjects described their posttreatment menstrual volume as heavy. The clinical significance of this is uncertain, as no laboratory evaluations were done in this study. However, heavy bleeding has not been a safety concern with the approved LNG emergency contraceptive products.*
- *In Study HRA 2914-509, no decrease in mean hemoglobin volume was observed.*

Based on pooled data, the mean increase in cycle length in subjects who took UA in the phase 3 trials was 2.5 days. Seven percent of subjects had a decrease in cycle length by a week or more and 19% had an increase in cycle length greater than one week. A total of 9% of subjects reported intermenstrual bleeding but in the majority of these

subjects, the bleeding was described as spotting. Heavy intermenstrual bleeding was reported in only 0.4% (11/2,637) subjects.

Table 26 Menstrual Cycle Changes, Pooled Phase 3 Data

Cycle Parameter	Ulipristal (n=2,488)
Mean (SD) Duration of Menstrual Cycle (days)	31.4 (9.5)
Mean Change (SD) from Average Cycle Length (days)	2.5 (9.4)
Treatment Cycle Changes (%) Decrease > 7 days Increase > 7 days	 7 19
Intermenstrual Bleeding	9

Source: Adapted from Summary of Clinical Safety, Table 2.7.4-9, Page 27.

Medical Reviewer's Comment

- *Posttreatment menstrual volume was not studied in the pooled data.*

Amenorrhea

Subjects who were not pregnant and had not experienced menses at Follow-Up Visit 2 entered the amenorrhea follow-up portion of the study. A total of 7 subjects underwent clinical investigations for amenorrhea because they had an increase in cycle length greater than 60 days. No serious pathology was found.

HRA 2914-509: Three subjects underwent clinical investigation. One was diagnosed with polycystic ovarian disease and her menses returned in 109 days. Another subject had no listed diagnosis and return of menses in 102 days. The third subject's menstrual outcome was unknown.

HRA 2914-513: Four ulipristal-treated subjects underwent clinical amenorrhea workup. One patient was diagnosed with polycystic ovarian syndrome. Another subject had return of menses in 86 days. The remaining two subjects were lost to follow-up.

7.4.2 Laboratory Findings

Clinical laboratory testing was only performed in the HRA 2914-509 trial. A total of 112 subjects had screening and end-of-study clinical laboratory results performed. No decrease in the mean hemoglobin value was observed. Only three subjects with normal values at screening had hemoglobin values slightly below the lower limit of normal at the end of the study. One subject with a normal hepatic panel at screening presented

an isolated and moderate increase in ALT and in AST (ALT 74, nl < 55; AST 88, nl < 45) 12 days after UA intake. The event was not reported as an AE. Repeat enrollers in the phase 3 program had no abnormal liver function results. For six subjects, changes from screening laboratory test values were assessed by the investigator as clinically meaningful and reported as AEs (three subjects with elevated serum potassium levels; and one each with elevated creatine kinase, white blood cell count, and glucose). No subject required treatment for her laboratory abnormality. All of these changes were considered by the investigators as not related or with unknown relationship to the study medication.

No clinical lab parameters were obtained in Study HRA 2914-513.

Medical Reviewer's Comments

- *No decrease in the mean hemoglobin value was observed between screening and the end of study. Few subjects had changes in laboratory values judged clinically significant by the investigator and reported as adverse events.*
- *There were no changes in the biochemical parameters (complete blood count, liver and renal function, lipids, and random glucose) in the women monitored before and after treatment that were considered as clinically significant.*

7.4.3 Vital Signs

No clinically significant vital sign abnormalities were reported.

7.4.4 Electrocardiograms (ECGs)

Electrocardiograms were not obtained in the clinical trials.

7.4.5 Special Safety Studies/Clinical Trials

No special safety studies other than the clinical trials were performed.

7.4.6 Immunogenicity

No immunogenicity studies were performed.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

This is a single dose product, so dose dependency for adverse events was not evaluated. The dosage strength used in the phase 3 trials was based on efficacy considerations.

7.5.2 Time Dependency for Adverse Events

Exploration for time dependency of adverse events was not performed.

7.5.3 Drug-Demographic Interactions

This product is indicated for use only in women of childbearing age. There is no evidence that the safety or efficacy of this product is significantly affected by age, race or ethnicity. The relationship of body weight to efficacy is discussed in Section 6.1.7 of this review.

7.5.4 Drug-Disease Interactions

No specific drug-disease interaction studies were performed.

7.5.5 Drug-Drug Interactions

No specific *in vivo* drug interaction studies have been performed with UA. *In vitro* data indicate that the metabolism of UA is predominantly mediated by CYP3A4.

Concomitant administration of potent CYP3A4 inhibitors may inhibit the metabolism of UA and cause an increase in plasma levels. Concomitant administration of potent CYP3A4 inducers may reduce plasma concentrations of UA, which might result in a decrease in efficacy.

Medical Reviewer's Comment

- *Information regarding the effect of CYP3A4 inhibitors and inducers should be included in the label.*

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

No human carcinogenicity studies were performed.

7.6.2 Human Reproduction and Pregnancy Data

No studies have been performed on the use of UA in pregnant women, but data on inadvertent exposure of very early pregnancy to UA in clinical trials indicate no particular safety issues.

The Applicant reported, as of June 17, 2010, a total of 113 pregnancies in women exposed to ulipristal in its safety database (92 occurred in the clinical development program and 21 were reported via post-marketing surveillance).

In the clinical development program, 92 women exposed to ulipristal became pregnant (two in the phase 1 program, 41 in two phase 2 studies, and 49 in the two phase 3 primary trials). Outcome data were available for 82 pregnancies. For these 82 pregnancies, outcome information is as follows:

- 60 subjects (73%) had induced pregnancy terminations
- 15 subjects (18%) had spontaneous abortions, and

- 7 subjects (9%) had live births
    - Five live births were reported as normal
    - One infant had optic nerve hypoplasia and developmental delay
    - One unknown outcome

In addition, ten women (11%) who became pregnant were lost to follow-up. There were no ectopic pregnancies.

The following provides further details of pregnancies in ulipristal-treated subjects in the phase 3 trials, which evaluated the to-be-marketed ulipristal product:

Study HRA 2914-509: Of the 29 ulipristal-treated subjects who became pregnant, 16 elected to have an induced termination and six reported spontaneous abortions. Of the remaining seven subjects, five subjects were reported as lost to follow-up, one had a normal live birth, and one delivered a female infant diagnosed with optic nerve hypoplasia (Subject 022-012). The subject was a 22 year old who conceived during the study. She was hypothyroid (at times uncontrolled) and taking thyroid replacement medication. Her baby was born on (b) (6) and had "problems with vision and psychological issues." The baby exhibited delayed gross motor skills associated with visual difficulties starting at two months of life. Magnetic resonance imaging (MRI) of the head at eight months of age showed reduced caliber of the optic nerve; endocrine workup, EEG, and myasthenia gravis testing were unremarkable. Visual impairment is ongoing with plans for a repeat MRI at two years of age (b) (6) An updated narrative summary was included in the 120 Day Safety Update Report for Subject 022-012. The site investigator assessed the relationship to study medication as not suspected and the SAE as unrelated to study procedures.

Study HRA 2914-513: Of the 20 ulipristal-treated subjects who became pregnant, 15 (75%) elected to have induced terminations and five (25%) had spontaneous abortions.

The Applicant has recently learned of one pregnancy in a healthy subject participating in a multiple-dose pharmacokinetics study conducted by a different sponsor. A pelvic ultrasound showed a twin pregnancy at approximately seven to eight weeks of gestation. The pregnancy is ongoing as of May, 2010, with an estimated delivery date in October, 2010.

In clinical studies no ectopic pregnancies were observed, but the number of pregnancies is too low to allow any definitive conclusion.

The outcomes of the 21 pregnancies reported in postmarketing reports since approval of ulipristal by the EMA are:

- 14 are ongoing normal pregnancies
- 2 were electively terminated
- 1 resulted in a spontaneous abortion
- 4 are lost to follow-up

Medical Reviewer's Comments

- *In contrast to progestins, progesterone receptor agonist/antagonists do not appear to have an effect on tubal motility (Gazvani, 1998; Guemzell, 2004). If tubal motility is not affected, one would not expect an increase in ectopic pregnancies with UA.*
- *It is difficult to determine the prevalence of spontaneous abortion in ulipristal-exposed subjects because 11 of 92 pregnancies (12%) were lost to follow-up. The actual spontaneous abortion rate could have ranged between 14% (assuming that none of these 11 pregnancies resulted in spontaneous abortion) to 27% (assuming all of these 11 pregnancies resulted in a spontaneous abortion). The generally reported prevalence of spontaneous abortion with a recognized pregnancy in the first trimester is approximately 15% - 20% (Warburton and Fraser, 1964, Alberman, 1988).*

7.6.3 Pediatrics and Assessment of Effects on Growth

This drug is not indicated for premenarchal females. The Pediatric Research Committee (PeRC) agreed that the Pediatric Research Equity Act (PREA) was waived for premenarchal females, and was fulfilled for postmenarchal females by extrapolation of data from adults (in addition to approximately 40 16-18 year olds included in Study 513). A postmarketing study on use in adolescents will be required to gain additional information on the safety of ulipristal use, particularly with respect to alterations in the menstrual cycle in adolescents.

The effects of UA on an exposed fetus are not well characterized in humans. A postmarketing study of pregnancy outcomes following exposure to ulipristal (e.g., contraception failures) will be a postmarketing requirement.

Use by lactating women will be discouraged in labeling due the lack of data about potential infant exposure through breast milk. A PK study to evaluate possible excretion of ulipristal into breast milk will be a postmarketing requirement.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

These issues were not addressed in the submission.

Medical Reviewer's Comment

- *This drug is indicated only for single dose administration. This would make significant issues of overdose, abuse and withdrawal unlikely.*

7.7 Additional Submissions / Safety Issues

A 120 Day Safety Update Report (PSUR) was received on 2/16/10 (S-0007). The report covered the period of time from 5/15/09 to 11/15/09.

During the period from 5/15/09 to 11/15/09, the estimated sales were approximately (b) (4) (each containing one 30 mg tablet) of the drug. Therefore, the estimated number of patients exposed is approximately (b) (4). No new safety findings were identified and no regulatory action was taken for safety reasons.

During the review period 53 subjects were exposed to Ellaone in HRA Pharma sponsored clinical trials.

In Europe, ulipristal acetate is co-developed by HRA Pharma and PregLem SA. PregLem SA is responsible for the development of UA (5 and 10 mg tablet) for the treatment of uterine myoma. Three studies were ongoing during the covered period. The cumulative estimation of the patients exposed to UA in these studies was approximately 460 subjects.

Outside the European Union, the Population Council sponsors studies of UA vaginal ring delivering a daily dose of 1500 or 2500 µg for regular contraception in Chile, the Dominican Republic and the USA. A total of 25 patients were exposed to UA in these Population Council-sponsored studies.

During the covered period, two medically confirmed serious adverse events were reported in clinical studies sponsored by PregLem SA, Geneva, Switzerland. PregLem SA is studying the safety and efficacy of UA as pre-operative treatment of symptomatic fibroids. One SAE involved the shrinkage of a fibroid, which caused it to become pedunculated and protrude through the cervical os. A transvaginal myoma resection was performed. A second serious adverse event involved the appearance of a new subserosal uterine myoma during treatment. This myoma was excised laparoscopically and was histologically benign.

One non-medically confirmed case report was collected within the covered period. This case was considered as nonserious and involved a female patient who experienced moderate abdominal pains after UA intake.

A “pregnancy registry” was established by the Applicant prior to launching the product to collect information on pregnancies exposed to UA. While not a true registry intended for systematic collection of all possible pregnancy reports, a dedicated internet website (http://www.ellaone-registry.com) has been designed, accessible in all local languages of the countries where Ellaone has been launched. By the end of the PSUR report period (11/15/09), this registry was accessible in France, the United Kingdom, Germany, Belgium, Luxembourg, the Netherlands, and Sweden. A Dear Doctor letter written in local language was mailed to all general practitioners and gynecologists of those countries to inform them about this registry and encourage them to report pregnancies exposed to UA. During the PSUR reporting period, no cases of pregnancy exposure had yet been reported via the Ellaone pregnancy registry.

The safety information collected during the reference period did not modify the safety profile of the UA. No new area of interest has been identified.

Proposed Postmarketing Requirements
Accidental exposure to UA during pregnancy has unknown consequences. Data on newborns from mother's exposed to UA during pregnancy also is limited. Recognizing this, the Division made the following recommendations to the Applicant on 7/14/2010 regarding proposed postmarketing requirements (PMR).

1. Pregnancy outcome study - We ask that you add a US component to your planned European pregnancy outcomes study.
- The applicant agreed to add a US component to the planned European pregnancy outcomes study.

2. Adolescent study - We ask that you add a US component to your planned UK/Sweden study of use in adolescents, and that you enroll at least 50 (completers) under the age of 16 over the full study (these do not necessarily have to be US subjects).
- The applicant agreed to add a US component to the planned adolescent study and to enroll at least 50 (completers) under the age of 16 over the full study.

3. Lactation study – The Applicant's planned lactation study to be conducted in Chile appears likely to fulfill this PMR.

4. Study of pregnancy complications following deliberate or inadvertent exposure during pregnancy (e.g., off-label use for indications other than emergency contraception, inadvertent administration to a woman with an unrecognized pregnancy, periconceptional exposure of a pregnancy that follows emergency contraception failure). We are particularly interested in evaluating any potential safety signals of complications of pregnancy loss, such as hemorrhage, infection, and need for surgical procedure such as D&C.
- The Applicant proposed to revise the protocol of the pregnancy outcome study so that sufficient data will be collected regarding spontaneous abortion, medical history, pregnancy history, exposure to other drugs, and the presence of risk factors for spontaneous abortion. Sufficient detailed data regarding complications of pregnancy loss will be collected so that a subsequent case-control component can be done if there appears to be a signal of concern.

8 Postmarket Experience

Authorization for marketing UA in the European Union was granted by the EMA on 5/15/2009. UA for the indication of emergency contraception within 120 hours (5 days) of unprotected sexual intercourse or contraceptive failure." is currently approved in 30 countries (European Union, Norway, Iceland and Lichtenstein

As part of the EMA's approval of UA, the Applicant committed to addressing the safety issues associated with the use of ulipristal with a pharmacovigilance program in Europe. This program includes routine pharmacovigilance complemented by targeted activities such as:

- Use of a specific report form for spontaneously reporting pregnancy outcomes.
- Facilitate collection of spontaneous reports of exposed pregnancies via a web-based interface
- Consolidate all information on pregnancy exposure in a global database
- A study targeting 1,000 prescribers in multiple EU countries to obtain clinical follow-up information on pregnancies exposed to ulipristal.

The Applicant also intends to monitor for off-label use by:

- Prescribers' self-reporting of off-label use.
- A study to identify off-label prescriptions using information from prescription registries in countries where it is considered feasible. This will be done after one to two years of marketing, depending on the level of ulipristal use.

9 Appendices

9.1 Literature Review/References

Both phase 3 trials have been published in the clinical literature:

- The Lancet, Volume 375, Issue 9714, Pages 555 -562, 13 February 2010, Ulipristal acetate versus levonorgestrel for emergency contraception: a randomized non-inferiority trial and meta-analysis
- Obstet Gynecol 2010;115:257-63, Ulipristal Acetate Taken 48-120 Hours After Intercourse for Emergency Contraception

9.2 Labeling Recommendations

Labeling is currently under review.

Medical Reviewer's Comments

- *Terminology describing the Mechanism of Action, (Section 12.1) is being discussed.* (b) (4) *As the exact mechanism of action of UA is not really known, the Division prefers to retain this language.*
- *The Division of Medication and Error Prevention and Analysis (DMEPA) found the name Ella acceptable.*

9.3 Advisory Committee Meeting

An Advisory Committee Meeting was held on June 17, 2010. The following questions were submitted to the Committee for consideration. Below is a list of the questions- and the Committee vote.

Questions to the Committee

1. Has the Applicant provided sufficient information to conclude that ulipristal reduces the likelihood of pregnancy when taken within 120 hours after unprotected intercourse or a known or suspected contraceptive failure?

   Yes-11 *No-0* *Abstain-0*

   - *Committee members noted that the efficacy data was compelling and voted unanimously that the Applicant provided sufficient information to conclude that ulipristal reduces the likelihood of pregnancy when taken within 120 hours after unprotected intercourse or a known or suspected contraceptive failure.*

2. Has the Applicant provided sufficient information to conclude that the safety profile for ulipristal is acceptable for the proposed indication?

   Yes-11 No-0 Abstain-0

   - *The committee came to a consensus that the applicant provided sufficient information to conclude that the safety profile for ulipristal is acceptable for the proposed indication. Committee members commented that additional information regarding information on risk in pregnancy is needed and recommended that this be addressed in the postapproval period.*
   - *Several Advisory Committee members noted that there is not yet enough information on risks of taking ulipristal in pregnancy and that this information needs to be addressed by postmarketing pharmacovigilance.*

3. Should product labeling include any recommendations on use in specific subpopulations (e.g., women with a BMI > 30 kg/m^2 because of reduced efficacy in heavier women)? If yes, what do you recommend?

This question was not designed as a voting question, but the Committee did provide the following responses:

Yes-5 No-6 Abstain-0

- *Committee members commented that patients and providers should be educated on use in women with a BMI>30 kg/m^2 and should be informed that efficacy cannot be confirmed in this BMI>30 kg/m^2 population.*
- *Some committee members also expressed concerns that including information about BMI in women of higher BMI in labeling may discourage heavier weight women from using this product. It was discussed that women need to be aware that little data exists regarding the effect of weight on efficacy and that this would not unfairly bias potential users and prescribers against this product, as compared to other products in which there is also little efficacy data for use in this population.*

4. Is there a need for measures beyond product labeling/healthcare provider education to address potential off-label use of ulipristal? If yes, what do you recommend?

   Yes-0 No- 11 Abstain-0

   - *The committee voted unanimously "no" to the question of whether there is a need for measures beyond product labeling/healthcare provider education to address potential off-label use of ulipristal.*

5. Are the following Risk Management elements adequate if ulipristal were to be approved for marketing in the U.S.? If not, what additional elements would be needed?

A. Labeling to recommend pregnancy testing prior to dosing if pregnancy cannot be excluded by history or examination

B. Pharmacovigilance monitoring of spontaneous reports for pregnancy outcomes

C. Postmarketing requirements:

a. Expansion to the US of the planned European study to obtain clinical follow-up data on pregnancy outcomes from women exposed to ulipristal

b. Retrospective survey of hospitals and providers to evaluate complications of pregnancy loss following the use of ulipristal (e.g., bleeding, infection)

- *Committee members commented that pregnancy testing would likely be done in practice, with comments noting that this should not be required.*
- *It was noted that the labeling should be restricted for use by lactating mothers as data on the possible exposure to breastfed infants are not available.*
- *The Committee noted that monitoring via pharmacovigilance was problematic but that no further measures were needed. However, the Committee was in agreement with the planned expansion study to the US of the planned European studies.*

APPENDIX 1

Primary Phase 3 Clinical Trial, HRA 2914-509: Summary of Study Protocol

Title
"A Prospective, Open-Label, Single Arm, Multicenter Study to Evaluate the Efficacy, Safety and Tolerability of CBD-2914 as Emergency Contraception When Taken Between 48 Hours and 120 Hours of Unprotected Intercourse"

Objectives
Primary:

- The primary objective is to demonstrate that the pregnancy rate observed after taking CDB-2914 30 mg between 48 hours and 120 hours of unprotected intercourse is statistically significantly lower than the estimated expected pregnancy rate in the absence of emergency contraception.

Secondary:

- To demonstrate that the pregnancy rate observed after taking CDB-2914 30 mg between 48 hours and 120 hours of unprotected intercourse is statistically significantly lower than 4% considered as a clinical irrelevance threshold
- To analyze the trend in pregnancy rates over time since the time of unprotected intercourse
- To estimate the contraceptive effectiveness (prevented fraction) of CDB-2914 30 mg
- To assess the impact of CDB-2914 30 mg on the menstrual cycle
- To evaluate the safety and tolerability profile of CDB-2914 30 mg

Inclusion Criteria

- Aged 18 years or more
- Menstruating women with regular menstrual cycle between 24 and 35 days and intra-individual variations less than or equal to 5 days
- Request emergency contraception between 48 hours and 120 hours after unprotected intercourse as defined by lack of contraceptive use, or condom breakage (including condoms lubricated with spermicide) or other barrier contraceptive method failure
- No current use of hormonal contraception and having had at least one complete menstrual cycle (2 menses) since having stopped hormonal contraception
- For women with a recent history of Depo Provera use, the most recent injection must have been at least 9 months before study entry and followed by at least one complete menstrual cycle (2 menses)
- Willing to not use hormonal methods of contraception until study completion

- At least one complete menstrual cycle (2 menses) post miscarriage, delivery or abortion
- Able to provide informed consent
- Give voluntary, written informed consent, and agree to observe all study requirements (the subject needs to be available for follow-up over the next 6 weeks)
- Willing to abstain from further acts of unprotected intercourse during participation in the study and until pregnancy status has been ascertained

Exclusion Criteria

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

Study Drug

- Ulipristal acetate (CDB-2914): 1 tablet containing 30 mg

Study Schedule

The Treatment visit is composed of two phases: the Screening phase and the Treatment phase.

Day 1: Treatment Visit – Screening Phase

- Women presenting for emergency contraception earlier than 48 hours post unprotected intercourse will be instructed to take an approved emergency contraceptive product
- HSUP test
- Serum for a β HCG pregnancy test will be obtained and performed only in case of a pregnancy detected during the current cycle at Follow-Up 1 or 2;
- Collect menstrual/coital history including date of onset of last menstrual period, average cycle length, expected date of next menses, date and time of all acts intercourse in the current cycle and methods of contraception used, if any,

description of the act of unprotected intercourse which motivated request for emergency contraception.
- Collect blood sample for safety laboratory safety analysis only for all repeat enrollments in all sites and a selection of women in designed sites
- Collect menstrual/coital history

Day 1: Treatment Visit – Treatment phase
- HSUP performed
- Dispense study medication to the subject for immediate intake in the presence of medical staff, and record time of intake;
- Inform the subject to contact the clinic immediately in case she vomits within 3 hours of taking study medication. Subject should then be instructed to take an approved emergency contraceptive product
- Schedule Follow-Up Visit 1 (to take place 5 to 7 days after expected next menses
- Give the home diary calendar
- Give condoms to the subject and remind her not to have unprotected intercourse during her participation in the clinical trial until pregnancy status have been definitively ascertained

Follow-Up Visit 1 (5-7 days after expected onset of menses)
- HSUP test positive and β HCG positive:
    - Quantitative serum β HCG ; if it is positive → TVU within 1 week with additional sonograms as needed for dating (+/- 3 days)
    - Assay the frozen pre-treatment serum sample for β HCG concentration (quantitative β HCG)
    - Follow-up of pregnancy until term/outcome
- HSUP test negative and menses resumed → study completion
- HSUP test negative but menses not resumed → Follow-up visit 2 scheduled one week later

Follow-Up 2 (12-14 days after expected onset of menses)
- HSUP test positive and β HCG positive:
    - Quantitative serum β HCG ; if it is positive → TVU within 1 week with additional sonograms as needed for dating (+/- 3 days)
    - Assay the frozen pre-treatment serum sample for β HCG concentration (quantitative β HCG)
    - Follow-up of pregnancy until term/outcome
- HSUP test negative and menses resumed → study completion
- HSUP test negative but menses not resumed → serum β HCG performed and amenorrhea follow-up initiated.

Schedule of Events (Study HRA 2914-509)

	Treatment Visit			
Study procedure	Screening Phase	Treatment Phase	Follow-Up Visit 1	Follow-Up Visit 2 *(if required)*
Study day	Day 1	Day 1	5-7 days after expected menses	12-14 days after expected menses
Informed consent	X			
High sensitivity urine pregnancy (HSUP) test	X		X	X
Inclusion / exclusion criteria	X			
Current cycle length and coital history	X			
Blood sample for serum β-hCG pregnancy test	X [a]		X [b]	X [c]
Blood sample for laboratory safety parameters	X [d]		X [d]	
Treatment intake		X		
Demographics		X		
Gynecological history		X		
Medical history		X		
Transvaginal ultrasound			X [e]	X [e]
Vaginal bleeding / Coital calendar			X	X
Pregnancy notification			X	X
Prior & concomitant Treatments		X	X	X
Adverse events		X	X	X
Amenorrhea follow-up				X [f]
Study completion			X [g]	X [g]
Pregnancy follow-up			X	X

a. To be frozen and assayed later only if pregnancy was diagnosed at Follow-Up Visits 1 or 2.
b. To be performed if urine pregnancy test was positive at Follow-Up Visit 1.
c. To be performed if urine pregnancy test was positive at Follow-Up Visit 2 or if urine pregnancy test was negative but menses had not resumed at Follow-Up Visit 2.
d. To be performed only for all repeat enrollments and a selection of women at designated sites.
e. To be scheduled within one week if pregnancy was detected at Follow-up visit 1 and as soon as possible if pregnancy was detected at Follow-Up Visits 2.
f. To be initiated if menses did not occurred at Follow-Up Visit 2.
g. To be performed when pregnancy status was ascertained and when amenorrhea investigations (if any) were performed.

Source: Clinical Study Report, Table 1, pg. 15-16.

POSITIVE URINARY PREGNANCY TEST FOLLOW-UP

If pregnancy is confirmed by positive serum β HCG pregnancy test:

- Pretreatment serum sample is assayed for β HCG concentration
- Transvaginal ultrasound within 1 week. If the pregnancy can not be dated precisely (+/- 3 days), schedule additional ultrasound(s) as needed.
- Pregnancy follow-up until term

AMENORRHEA FOLLOW-UP

- The subject is instructed to refrain from hormonal contraceptives until spontaneous menses have resumed;
- Urine pregnancy test to be performed 30 days and 60 days after expected onset of menses.
- The subject will be called every 2 weeks for follow-up
- If persistent amenorrhea and negative urine pregnancy test 60 days after expected menses → prolactin, TSH, FSH, LH and estradiol assays; and transvaginal ultrasound

Safety measurements

- Adverse events
- Change in cycle length during treatment cycle compared to baseline
- Incidence and duration of intermenstrual bleeding
- Incidence of amenorrhea and laboratory safety parameters

APPENDIX 2

Primary Phase 3 Clinical Trial, HRA 2914-513: Summary of Study Protocol

Title

"A Prospective, Randomized, Single Blind, Multicenter Study to Compare the Efficacy, Safety and Tolerability of CDB-2914 with Levonorgestrel as Emergency Contraception within 120 Hours of Unprotected Intercourse"

Objectives

Primary:

- The primary objective is to demonstrate that the pregnancy rate observed after taking CDB-2914 30 mg within 72 hours of unprotected intercourse is statistically significantly lower than the estimated expected pregnancy rate in the absence of emergency contraception

Secondary:

- To demonstrate the non-inferiority of CDB-2914 30 mg versus levonorgestrel 1.5 mg as emergency contraception within 72 hours of unprotected intercourse. Should non-inferiority be demonstrated, superiority will be tested
- To demonstrate that the pregnancy rate observed after taking CDB-2914 30 mg within 120 hours of unprotected intercourse is statistically significantly lower than the estimated expected pregnancy rate in the absence of emergency contraception
- To demonstrate the non-inferiority of CDB-2914 30 mg versus levonorgestrel 1.5 mg as emergency contraception within 120 hours of unprotected intercourse. Should non-inferiority be demonstrated, superiority will be tested.

- To compare the trend in pregnancy rates over time since intercourse of CDB-2914 30 mg to levonorgestrel 1.5 mg
- To compare the estimated contraceptive effectiveness (prevented fraction) between treatment groups
- To assess the impact of CDB-2914 30 mg on the menstrual cycle compared to levonorgestrel 1.5 mg
- To evaluate safety and tolerability profile of CDB-2914 30 mg in comparison to levonorgestrel 1.5 mg

Inclusion Criteria

- Aged 16 years or more in UK sites and 18 years or more in US and Canada sites
- Menstruating women with regular menstrual cycle between 24 and 35 days and intra-individual variations less than or equal to 5 days
- Request emergency contraception within 120 hours after unprotected intercourse as defined by lack of contraceptive use, or condom breakage (including condoms lubricated with spermicide) or other barrier contraceptive method failure
- No current use of hormonal contraception and having had at least one complete menstrual cycle (2 menses) since having stopped hormonal contraception
- For women with a recent history of Depo Provera use, the most recent injection must have been at least 9 months before study entry and followed by at least one complete menstrual cycle (2 menses)
- Willing to not use hormonal methods of contraception until study completion
- At least one complete menstrual cycle (2 menses) post miscarriage, delivery or abortion
- For women who present more than 72 hours after intercourse, decline the insertion of an IUD for emergency contraception and/or have contraindications to IUD insertion
- Able to provide informed consent
- Give voluntary, written informed consent, and agree to observe all study requirements (the subject needs to be available for follow-up over the next 6 weeks)
- Willing to abstain from further acts of unprotected intercourse during participation in the study and until pregnancy status has been ascertained

Exclusion Criteria

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

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

Study Drugs

- Ulipristal acetate: 1 tablet containing 30 mg
- Levonorgestrel (Levonelle® 1500): 1 tablet containing 1.5 mg

Study Schedule

The Treatment visit is composed of two phases: the Screening phase and the Treatment phase.

Day 1: Treatment Visit – Screening Phase

- For women who present after 72 hours, discuss the possibility of fitting an IUD for emergency contraception; only if IUD is declined or contraindicated, invite woman to enroll;
- HSUP test
- Serum β HCG pregnancy test only performed in case of a pregnancy detected during the current cycle at Follow-Up 1 or 2;
- Collect menstrual/coital history including date of onset of last menstrual period, average cycle length, expected date of next menses, date and time of all acts intercourse in the current cycle and methods of contraception used, if any, description of the act of unprotected intercourse which motivated request for emergency contraception.

Day 1: Treatment Visit – Treatment phase

- Emergency contraception intake
- Given urine collection tubes and home diary calendar
- Schedule phone call for Follow-Up 1 (to take place 5 to 7 days after expected next menses
- If the subject has vomiting within 3 hours of taking study medication, she will take an approved EC product
- Condoms dispensed and the subject instructed not to have unprotected intercourse during her participation in the clinical trial until pregnancy status have been definitively ascertained

Follow-Up 1 (5-7 days after expected onset of menses)

- First Telephone Contact (5-7 days after expected onset of menses):

  - Remind subject to collect urine (preferably early in the morning) and send sample
  - Collect information on menstrual bleeding
  - Adverse events and coital calendar assessed.
  - Collect/update concomitant treatments
  - Ask subject to send the first part of the home diary calendar to the site

- Second Telephone Contact (to be performed as soon as the result of HSUP test is known)
  - Inform subject of the result of pregnancy test
    - If HSUP test negative and menses have resumed, the study completion form is completed
    - If HSUP test negative but menses have not resumed, schedule Follow-Up 2 one week later
    - If HSUP is positive → β HCG and transvaginal sonogram

Follow-Up 2 (12-14 days after expected onset of menses)

- First Telephone Contact (12-14 days after expected onset of menses):
  - Remind subject to collect urine (preferably early in the morning) and send sample
  - Collect information on menstrual bleeding
  - Adverse events and coital calendar assessed.
  - Ask subject to send the home diary calendar to the site

- Second Telephone Contact (to be performed as soon as the result of HSUP test is known)
  - Inform subject of the result of pregnancy test
    - If HSUP test negative and menses have resumed, the study completion form is completed
    - If HSUP test negative but menses have not resumed, schedule clinic visit for a β HCG and initiate an amenorrhea follow-up.
    - If HSUP is positive → β HCG and transvaginal sonogram

POSITIVE URINARY PREGNANCY TEST FOLLOW-UP

If pregnancy is confirmed by positive serum β HCG pregnancy test:

- Pretreatment serum sample is assayed for β HCG concentration
- Transvaginal ultrasound within 1 week. If the pregnancy can not be dated precisely (+/- 3 days), schedule additional ultrasound(s) as needed.
- Follow-up of pregnancy until term/outcome
- Follow-up baby's health until the age of 1 year.

AMENORRHEA FOLLOW-UP

- The subject is instructed to refrain from hormonal contraceptives until spontaneous menses have resumed;
- Urine pregnancy test to be performed 30 days and 60 days after expected onset of menses.
- The subject will be called every 2 weeks for follow-up
- If persistent amenorrhea and negative urine pregnancy test 60 days after expected menses → prolactin, TSH, FSH, LH and estradiol assays; and transvaginal ultrasound

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22474	ORIG-1	LABORATOIRE HRA PHARMA	Ella , Ulipristal Acetate

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

/s/

RONALD J ORLEANS
08/06/2010

LISA M SOULE
08/06/2010

I concur with Dr. Orleans' conclusions and recommendation that NDA 22-474 be approved for the indication of emergency contraception within 120 hours after unprotected intercourse or contraceptive failure. I further agree that the specified postmarketing studies should be required as a condition of approval.