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*APPLICATION NUMBER:*  
**22-474**

**CROSS DISCIPLINE TEAM LEADER REVIEW**

## Cross-Discipline Team Leader Review

<b>Date</b>	August 12, 2010
<b>From</b>	Lisa M. Soule, M.D.
<b>Subject</b>	Cross-Discipline Team Leader Review
<b>NDA/BLA #</b>	22-474
<b>Applicant</b>	HRA Pharma
<b>Date of Submission</b>	October 15, 2009
<b>PDUFA Goal Date</b>	August 15, 2010
<b>Proprietary Name / Established (USAN) names</b>	ella ulipristal acetate
<b>Dosage forms / Strength</b>	Single dose, 30 mg oral tablet
<b>Proposed Indication(s)</b>	Prevention of pregnancy following unprotected intercourse or a known or suspected contraceptive failure
<b>Recommended:</b>	<i>Approval</i>

### 1. Introduction

This NDA seeks marketing approval for a new molecular entity (NME), ulipristal acetate, for the indication “prevention of pregnancy following unprotected intercourse or a known or suspected contraceptive failure.” Ulipristal is a progesterone agonist/antagonist, a pharmacologic class that is sometimes referred to as selective progesterone receptor modulator (SPRM). For this indication, ulipristal is administered as a single oral dose of 30 mg, to be taken as soon as possible, but no later than 120 hours after unprotected intercourse (UPI). Ulipristal has been approved in the EU for about a year, and a limited amount of postmarketing data is available.

Currently approved products for emergency contraception (EC) are limited to levonorgestrel (LNG) tablets, including Plan B (and its generic), with a dose regimen of two tablets of 0.75 mg LNG taken 12 hours apart, and Plan B One-Step, which is administered as a single 1.5 mg dose of LNG. These products are indicated for use within 72 hours of UPI, and are available over the counter (OTC) for women aged 17 and above, and by prescription only for women under age 17. Ulipristal would be the first marketed product to offer protection against pregnancy for up to 120 hours after UPI.

Ulipristal is in the same pharmacologic class as mifepristone, a product approved in the US for “the medical termination of intrauterine pregnancy through 49 days’ pregnancy.” In addition to administering the labeled dose of 600 mg of mifepristone, 400 µg of misoprostol must be taken two days later to achieve optimal efficacy in terminating the pregnancy. Nonetheless, due to the similarity of ulipristal to mifepristone, there has been interest in determining the potential of ulipristal to terminate an existing pregnancy if it were inadvertently administered to a woman with an unsuspected pregnancy, or used off-label for attempted medical termination of pregnancy. In addition, the fetal effects of exposure during pregnancy have not been well elucidated, although limited animal studies do not suggest a teratogenic potential.

The Applicant submitted two pivotal phase 3 trials to support the safety and efficacy of ulipristal for EC. Both studies met their primary efficacy endpoints, and the trial that used a LNG 1.5 mg comparator demonstrated that ulipristal is non-inferior to LNG 1.5 mg in preventing pregnancy. No significant safety issues were observed in the safety database of 2,764 women who received a single dose of the to-be-marketed formulation.

The major issues addressed in this review primarily involve needed postmarketing studies and labeling. Areas that required negotiation with the Applicant included:

- Labeling with regard to possible mechanisms of action of ulipristal in preventing pregnancy
- Labeling with regard to the impact of higher body mass index (BMI) on efficacy
- Commitment to conduct four required postmarketing studies to evaluate more fully safety issues that could not be definitively explored in premarketing studies, and to conduct a drug-drug interaction study as a postmarketing commitment.

## 2. Background

### 2.1 DESCRIPTION OF PRODUCT

Ulipristal is a progesterone agonist/antagonist (sometimes referred to as a SPRM) to be administered in a single 30 mg dose to provide EC within 120 hours after UPI. Ulipristal also has anti-glucocorticoid activities, and also binds to the androgen receptor with lower affinity, but has minimal affinity for estrogen or mineralocorticoid receptors. Progesterone is essential for the initiation and maintenance of pregnancy. In the normal menstrual cycle, progesterone facilitates the luteinizing hormone (LH) surge essential to ovulation and transforms the endometrium from a proliferative to secretory state. During pregnancy, progesterone inhibits myometrial contractility and maintains the uterus in a quiescent state.

Selective progesterone receptor modulators are pharmacologic agents that exert their activity by binding to progesterone receptors in different tissues in the body. The pharmacologic effects of individual SPRMs vary and are based on their relative agonistic and antagonistic effects in different tissues (e.g., ovary vs. endometrium). Progesterone receptor modulators are known to affect reproductive outcomes.

Ulipristal is in the same pharmacologic class as mifepristone, which is the only other approved progesterone agonist/antagonist product in the US. Mifepristone is indicated for medical termination of pregnancy, but is used concomitantly with misoprostol to attain optimal efficacy. Mifepristone is available through a restricted distribution program, due to the need for prescribers to be able to manage (or refer to a surgeon who can manage) an incomplete pregnancy termination. Safety signals noted with mifepristone appear specific to the indication, and are mainly hemorrhagic and infection-related complications of pregnancy termination.

Ulipristal was approved by the EMA under a centralized procedure in May 2009, and is now available in 30 countries under the trade name ellaOne<sup>®</sup> for EC “within 120 hours (5 days) of unprotected sexual intercourse or contraceptive failure.”

## 2.2 REGULATORY HISTORY

The initial IND for ulipristal was opened by the National Institute for Child Health and Human Development (NICHD) in 1995 (IND 49,381). In 2006, HRA Pharma licensed ulipristal from NICHD and became the sponsor of the IND. The Applicant and representatives of NICHD initially met with the Division of Reproductive and Urologic Products (DRUP) in April 2004, for an End of Phase 2 discussion. The Division recommended that phase 3 include a comparative study against an approved EC drug, using either non-inferiority or superiority as the endpoint, and that at least 50% of subjects be from US study sites. While the Applicant wanted to enroll subjects up to 120 hours after UPI, the Division requested that a sufficient number be enrolled within 72 hours to allow for demonstration of non-inferiority or superiority to the approved (72 hour) product. The Division also noted that two adequate and well-controlled studies are usually needed to support an NDA for a NME product.

(b) (4)



The Division agreed with the plan to exclude pregnancies identified as having started prior to treatment, but noted that all pregnancy data should be submitted in the NDA, as the Division would conduct its own evaluation of conception timing. The Division also agreed with the selection of a 4% pregnancy rate as indicating clinical relevance (i.e., a pregnancy rate above 4% would be considered unacceptable even if it were statistically significantly lower than the expected rate). The Division requested that study success should require both a statistically significantly lower observed pregnancy rate as compared to the expected rate, and as compared to 4%.

The Applicant and the Division met again in August 2006 to discuss the SPA comments. The Division agreed with the primary efficacy endpoint of pregnancy rate, to be compared to the expected pregnancy rate. The Division agreed that the modified intent to treat (mITT) population (defined as all subjects 35 years and under who have received EC, have a known pregnancy status and did not have a pre-treatment pregnancy) should be the primary efficacy population. An ITT analysis including all subjects who became pregnant, regardless of the

timing of conception was also requested. The Applicant agreed to the definition of study success proposed by the Division in the SPA comments.

The Applicant submitted several protocol amendments through 2007, and the Division provided comments in August 2007. DRUP noted again that it would review details of all pregnancies and might not agree with the Applicant's determination of which pregnancies were not compatible with EC failure. Analyses both including and excluding "not compatible" pregnancies were requested. The Division also authorized the importation of Levonelle into the US under IND 49,381, for use in the comparative study.

A preNDA meeting was held in December 2008. The Division noted that all nonclinical studies needed to assess the safety of ulipristal should be submitted in the NDA submission, not during the review cycle. DRUP noted again that it might consider the analysis population that included "not compatible" pregnancies (i.e., the proposed mITT2 population) to be the appropriate primary analysis population.

An additional guidance meeting requested to discuss the contents and format of the NDA was denied in June 2009; however, written responses to the Applicant's questions were provided in August 2009. (b) (4)

DRUP also requested that safety data be provided from all studies, including those that had evaluated lower doses than that to be marketed.

### **2.3 PRIMARY MEDICAL REVIEWER'S RECOMMENDATION FOR APPROVABILITY**

The primary reviewer, Dr. Ronald Orleans, stated in his review, dated August 7, 2010:

*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.*

Dr. Orleans further recommended that the Applicant conduct four studies as postmarketing requirements, including

- a pregnancy outcomes study to evaluate potential maternal complications and fetal and neonatal adverse outcomes in the event of exposure to ulipristal during pregnancy
- a case-control study to explore further the association of ulipristal with maternal complications of pregnancy loss, to be conducted if the pregnancy outcomes study suggests a signal of concern
- a study of use in adolescents, with particular attention to potential alterations to the menstrual cycle
- a study of the potential for excretion of ulipristal into breast milk

**Team Leader Comment**

**I concur with Dr. Orleans' recommendation for approval and for requiring the four specified postmarketing studies.**

### 3. CMC/Device

The primary Chemistry reviewer, Bogdan Kurtyka, Ph.D., made the following recommendations in his review dated June 25, 2010:

*This NDA has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product. An overall "Acceptable" site recommendation has been made from the Office of Compliance.*

*However, issues on labels/labeling have not been resolved. Therefore, from a CMC perspective, this NDA is not recommended for Approval in its present form.*

No postmarketing actions were requested.

The Drug Master File for this NME product was cross-referenced in this application, and a letter of authorization was provided by the DMF holder, (b) (4). The DMF was reviewed and found to be adequate. The drug product is a non-coated tablet to be made at two manufacturing sites, which were shown to produce bioequivalent products despite different manufacturing equipment. All excipients are USP/NF grade, are listed in the Inactive Ingredients Database, and amounts do not exceed previously approved levels. The batches used in clinical trials and stability batches are identical to the proposed commercial product. An expiry period of 36 months was granted; (b) (4) was found acceptable. Dr. Kurtyka noted that the Applicant provided sufficient information on raw material controls, manufacturing process and process controls and adequate specifications to assure consistent product quality of the drug substance and drug product. The limit for one impurity (b) (4) was noted to be above the ICH quantification threshold limit; this was discussed with the pharmacology/toxicology reviewer, who confirmed that this impurity (b) (4) is reasonable safe. Therefore the proposed limit was deemed to be acceptable. The tablets were shown to be sensitive to light, and labeling will warn about protecting from light. The container/closure system was found to be adequate.

Dr. Kurtyka recommended a categorical exclusion from environmental assessment. An overall recommendation of "Acceptable" was made on May 10, 2010 by the Office of Compliance.

CMC labeling revisions were made to the proposed label and to carton/container labeling, and were conveyed to the Applicant, who agreed to incorporate them. Agreement has been reached upon the established name of the product.

In an addendum to his review dated August 12, 2010, Dr. Kurtyka stated:

*Previous CMC Review #1 dated 25-JUN-2010 noted following labeling issues with a recommendation of "Non Approval" action.*

- *Established name and route of administration are missing from section #11 (Description) of the package insert*
- *Strength of dosage form not listed in section #16 (How Supplied/Storage and Handling) of the package insert*

*The sponsor submitted the updated labeling on 12-AUG-2010 and addressed above issues satisfactorily.*

*Therefore, from a CMC perspective, NDA 22-474 is now recommended for "Approval."*

As this is a NME product, concurrence was also required at the office level; Dr. Terrance Ocheltree, Director of the Division of New Drug Quality Assessment II, ONDQA, concluded the following in his memo dated August 12, 2010:

*I concur with the approval recommendation from a CMC perspective without any post marketing commitments.*

#### **4. Nonclinical Pharmacology/Toxicology**

The Applicant submitted a nonclinical program for ulipristal that included pharmacology studies, pharmacokinetic (PK) and toxicokinetic (TK) studies, general toxicology studies, acute and chronic (6 month) toxicology studies, genotoxicity studies, and reproductive toxicity studies. The TK profiles did not allow for accurate comparison to human exposure, due to use of Ctrough measurements, rather than AUC. Repeat toxicity studies showed the expected effects of an antiprogesterin/antiglucocorticoid agent, with primary effects on the reproductive and endocrine systems, and the liver. The NOAEL was 1 mg/kg in monkeys, with an exposure multiple of 0.65 on a  $\text{mg}/\text{m}^2$  basis compared to human clinical exposure. A NOAEL was not identified in rats.

The *in vitro* and *in vivo* genotoxicity assays were negative for mutagenicity or clastogenicity. Carcinogenicity testing in rats has not been completed, but a computational toxicity consult was requested. The consult response concluded that

*In considering the entire weight of evidence, ICSAS concludes that Ulipristal acetate is predicted to be negative for both rat and mouse carcinogenicity.*

Reproductive and developmental toxicity studies demonstrated reduction in pregnancy rates, reduced number of live pups, loss of post-implantation fetuses early after treatment, and early induction of parturition. The pharmacologic effects of ulipristal demonstrated in nonclinical studies include dose-dependent inhibition of ovulation, pregnancy and implantation rates, with reduction in number of conceptuses and increased number of resorptions. The ability of a single dose to interrupt an established pregnancy was not studied in the nonclinical program. When administered over four days to macaques, pregnancy terminations did not occur in any of five animals dosed at 0.5 mg/kg, but occurred in two of five animals dosed at 5 mg/kg. No malformations were noted in any surviving offspring. Teratogenicity was also not seen in rat and rabbit embryofetal studies using doses low enough not to completely block pregnancy. Studies of F1 reproduction demonstrated no adverse effects on sexual maturation, mating performance or fertility parameters.

The primary Toxicology reviewer, Jeffrey Bray, Ph.D., made the following recommendations in his review dated June 28, 2010:

***Recommendations on approvability:*** *Yes. Pharmacology recommends approval for emergency contraception for up to 120 hours following unprotected sexual intercourse.*

***Recommendations for nonclinical studies:*** *None.*

***Recommendations on labeling:*** *Nonclinical labeling in sections 8.1, 8.3, 13.1 and 13.2 require modification.*

As this is a NME product, concurrence was also required at the office level; Dr. Abby Jacobs, Associate Director of the OND Immediate Office Pharmacology/Toxicology concluded the following in her memo dated July 29, 2010:

1. *I concur that there are no pharm/tox issues affecting approval and that the pregnancy category is appropriate.*
2. *I have discussed my comments with the supervisor and they will be addressed as appropriate.*

**Team Leader Comments**

- **Dr. Bray provided labeling comments on the sections mentioned above to the Applicant and they were generally accepted by the Applicant. Dr. Bray found the Applicant's language in Sections 8.1 and 13.1 acceptable as contained in the revised labeling submitted on August 12, 2010. This is reflected in his memo dated August 13, 2010.**
- **Dr. Jacobs' comments related to minor labeling revisions, and the label was revised in accord with her recommendations.**

## **5. Clinical Pharmacology/Biopharmaceutics**

The Applicant submitted 16 clinical pharmacology studies, in addition to the four phase 2 and 3 clinical studies. These included eight studies of the distribution, metabolism and drug interaction potential, and eight pharmacokinetic (PK) and pharmacodynamic (PD) studies that characterized the mechanism of action of ulipristal for EC. These were reviewed by the primary Clinical Pharmacology Reviewer, Hyunjin Kim, Ph.D.

When ulipristal was under development by NICHD, the original drug formulation consisted of various doses of non-micronized ulipristal formulated in capsules. The initial pharmacology program and the phase 2 clinical trials were conducted using these capsules. After HRA Pharma licensed the rights to the compound, micronization was added as the last step of the manufacturing process to facilitate drug absorption. Based on results of early studies, the Applicant considered 50 mg non-micronized ulipristal to be the minimum dose that inhibited ovulation and altered the endometrium. The Applicant then conducted a comparative bioavailability study to bridge the different formulations used in the development of ulipristal. Although the final 30 mg micronized dose was not directly evaluated in this trial, compared to the non-micronized ulipristal formulation, micronized ulipristal provided greater bioavailability (mean C<sub>max</sub> was 95% higher and mean AUC was 40% higher for 10 mg micronized tablets as compared to 10 mg non-micronized capsules). For this reason, the 30 mg micronized tablet was developed as the to-be-marketed formulation with the objective of achieving the same absorbed dose as with the 50 mg non-micronized capsule that had been evaluated in phase 2 and which appeared to be efficacious. Both phase 3 clinical trials were conducted using the to-be-marketed 30 mg micronized formulation of ulipristal.

In addition, the Applicant conducted a single dose bioequivalence (BE) study of the to-be-marketed formulation showing that the products manufactured at two different manufacturing sites are bioequivalent.

Dr. Kim stated the following in his review dated July 9, 2010:

*The Division of Clinical Pharmacology 3, Office of Clinical Pharmacology finds the clinical pharmacology information submitted in NDA 022474 acceptable provided that an*

*agreement is reached between the sponsor and the Division regarding the language in the package insert.*

A phase 4 commitment was requested for an *in vivo* drug-drug interaction study of ulipristal with a CYP3A4 inducer. Dr. Kim and the Office of Clinical Pharmacology initially requested that this be done as a postmarketing requirement. However, as the concern to be addressed by this study related to the impact of CYP3A4 inducers on decreasing exposure to ulipristal and hence reducing efficacy, it was determined that a postmarketing commitment was the appropriate mechanism to request the study. This is documented in Dr. Kim's addendum to his review, dated July 23, 2010.

**Team Leader Comment**

**Dr. Kim provided a further addendum to his review dated August 12, 2010, that addressed the revised labeling submitted by the Applicant on August 12, 2010, which became the final agreed-upon version. He concluded that:**

*The Division of Clinical Pharmacology 3, Office of Clinical Pharmacology finds the NDA 022474 acceptable.*

## **5.1 Pharmacokinetics**

Ulipristal is highly protein-bound (>94%), and is metabolized predominantly by CYP3A4. No drug-drug interaction studies were conducted to evaluate the effect of concomitant administration with CYP3A4 inducers or inhibitors. A possible interaction with CYP3A4 inducers is of concern, because this could have the potential to reduce plasma concentrations and thereby efficacy of ulipristal. *In vitro* studies show ulipristal to have minimal potential for inducing or inhibiting CYP enzymes. Following a single dose, the maximum plasma concentrations of ulipristal and its active metabolite, 3877A, were reached (T<sub>max</sub>) within one hour of administration. The C<sub>max</sub> and AUC of ulipristal was more than twice that of 3877A. The half-life is about 32 hours.

Administration with food decreases ulipristal's absorption, resulting in 40-50% reduction in C<sub>max</sub> and a delayed T<sub>max</sub> of about two hours, but also increases the extent of absorption as seen by a 20-25% increase in AUC. However, the phase 3 studies were conducted with no restriction on dosing with respect to meals, so the clinical data support administration regardless of food intake.

No studies were conducted in subjects with renal or hepatic impairment.

## **5.2 Pharmacodynamics**

The pharmacologic action of ulipristal is mediated by its binding to the progesterone receptor. A number of studies were conducted to assess the effects of single dose administration at different phases of the menstrual cycle.

- In the mid-follicular phase (Study HRA 2914-505), ulipristal suppressed the growth of the lead follicle and increased the time to follicular collapse, thereby delaying ovulation. It also inhibited luteal phase endometrial maturation and decreased the plasma estradiol concentration.
- In the late follicular phase (Study HRA 2914-511), ulipristal reduced the incidence of follicular rupture and of the LH surge. The plasma concentration of progesterone, but

not of estradiol, was suppressed. The effect on follicular rupture was modified by the timing of dosing with respect to the LH surge, which triggers ovulation. If ulipristal was administered before the onset of the LH surge, 100% inhibition of follicular rupture was observed. If dosed after the onset of the LH surge, when rupture is imminent, 46% of follicles were inhibited. Of these subjects, 79% of those dosed before the LH peak was achieved had follicular rupture inhibited, while only 8% of those treated after the LH peak were inhibited. Therefore, it appears that ulipristal is very effective in blocking ovulation even when given after the LH surge has begun, up until the time of the LH peak. In contrast, LNG does not appear to delay or block follicular rupture if given after onset of the LH surge.

- In the early luteal phase (Study HRA 2914-506), a single dose of ulipristal reduced endometrial thickness, but did not affect the length of the menstrual cycle, or estradiol or progesterone levels.
- In the mid-luteal phase (Study HRA 2914-503), ulipristal did not affect the length of the luteal phase at doses above the to-be-marketed dose, but at about four-fold higher doses, the luteal phase was shortened and early and prolonged menses was observed.

## 6. Clinical Microbiology

A microbiology consult was not needed for this oral tablet; Dr. Kurtyka concluded that controls necessary for the manufacture of solid oral dosage forms are conducted in accordance with cGMPs to prevent microbial contamination. All results of microbiological tests performed on the drug product show no microbiological contamination.

## 7. Clinical/Statistical - Efficacy

### 7.1 OVERVIEW OF CLINICAL PROGRAM

As ulipristal was originally studied by the NICHD, and later licensed by HRA Pharma, the clinical development program includes both studies conducted by HRA Pharma (the Applicant) and studies sponsored by NICHD that are submitted in the form of publications. The latter include two phase 2 safety and efficacy studies that were conducted with earlier formulations of ulipristal. These are outlined in Table 1. These studies demonstrated that ulipristal was efficacious as an emergency contraceptive, and was non-inferior to the approved product of LNG given as two 0.75 mg doses. The studies also guided dose selection, as both of the 10 mg doses, whether micronized or non-micronized formulations, did not provide acceptable efficacy, while the 50 mg non-micronized dose was effective. As the Applicant moved forward in developing the to-be-marketed micronized formulation, the 30 mg micronized dose was taken into phase 3, as this was expected to provide similar exposure to that of the 50 mg non-micronized formulation.

**Table 1 Summary of Phase 2 Studies for Ulipristal**

Study Number	Primary Objective	Study Design	Treatment Groups	Efficacy Results # of Pregnancies Pregnancy Rate (95% CI)
<b>HRA2914-507</b> NICHHD <ul style="list-style-type: none"> <li>9/20/99 - 9/10/01</li> <li>7 US sites</li> <li>Randomized=1,672 -UPA=832* -LNG=840</li> <li>Completed=1,578 -UPA=792 -LNG=786</li> </ul>	Efficacy of UPA compared to LNG taken within 0-72 hrs of UPI	Prospective, Randomized Double-blind Multicenter Active-controlled Parallel group	UPA 50 mg non-micronized gelatin capsule, single dose/ placebo taken 12 hours apart  LNG 0.75 mg, 2 doses taken 12 hours apart	<u>UPA (n=792)</u> 12 pregnancies 1.52% (0.79, 2.63)  <u>LNG (n=786)</u> 14 pregnancies 1.78% (0.98, 2.97)  <u>Difference: UPA-LNG</u> -0.27% (-1.99, 1.42) Upper bound < 2.0  <u>Conclusion:</u> UPA non-inferior to LNG
<b>HRA2914-508</b> NICHHD <ul style="list-style-type: none"> <li>8/20/01 - 11/6/03</li> <li>9 US sites</li> <li>Randomized=1026 UPA 10 nm=214** UPA 10 m=399*** UPA 50 nm=413</li> <li>Completed=952 -UPA 10 nm=203 -UPA 10 m=365 -UPA 50 nm=384</li> </ul>	Efficacy and safety of two different doses of UPA taken within 0-72 hrs of UPI	Prospective, Randomized Double-blind Multicenter Active-controlled Parallel group	UPA 10 mg non-micronized capsule  UPA 10 mg micronized capsule  UPA 50 mg non-micronized capsule	<u>UPA 10 mg non-micronized (n=203)</u> 11 pregnancies 5.4% (2.7, 9.5) ****  <u>UPA 10 mg micronized (n=365)</u> 10 pregnancies 2.74% (1.32, 4.99)  <u>UPA 50 mg (n=384)</u> 5 pregnancies 1.30% (0.42, 3.02)

\* UPA = ulipristal

\*\* nm = non-micronized

\*\*\* m = micronized

\*\*\*\* Treatment group discontinued due to lack of efficacy

Source: NDA 22-474 submission, Tabular Listing of Clinical Studies 5.2

The primary clinical data submitted in this NDA are based on the two pivotal phase 3 safety and efficacy trials conducted by the Applicant. Study HRA 2914-509 (hereafter referred to as Study 509) was a prospective, multicenter, open-label, single-arm trial, conducted in the United States (US), evaluating the efficacy and safety of a single dose of ulipristal 30 mg administered 48 to 120 hours after unprotected intercourse or a contraceptive failure in women ages 18 years and older with regular menstrual cycles seeking EC. The primary endpoint was the observed pregnancy rate compared to the estimated expected pregnancy rate in the absence of EC. Study 509 enrolled 1,533 women aged 18 years and above at 40 US study sites.

Study HRA 2914-513 (hereafter referred to as Study 513) was a prospective, multicenter, randomized, single-blind (Applicant and subjects blinded; investigators unblinded), parallel group, comparative trial, conducted in the United Kingdom, Ireland, and the US, evaluating the efficacy and safety of a single dose of ulipristal 30 mg compared to LNG 1.5 mg administered 0 to 120 hours after unprotected intercourse or a contraceptive failure in women ages 16 years and older with regular menstrual cycles seeking EC. The primary endpoint was the observed pregnancy rate compared to the estimated expected pregnancy rate in the absence of EC after a single dose of ulipristal administered 0 to 72 hours after unprotected coitus; a

secondary endpoint evaluated the observed vs. expected pregnancy rate when EC was taken within 120 hours after UPI. Study 513 randomized a total of 2,221 women aged 16 years and above at 24 US study sites, 10 UK sites and one site in Ireland. Of these, 1,104 were randomized to ulipristal and 1,117 to LNG.

**Team Leader Comment**

**Study 509 had a primary endpoint limited to 0-72 hours following UPI because that is the approved time window for administration of LNG 1.5 mg. Women who presented more than 72 hours after UPI were eligible for inclusion only if they declined or had contraindications to insertion of a copper IUD (an approved product used in an off-label manner for EC).**

Entry criteria were similar for both trials and are detailed in Dr. Orleans' review, but briefly, included regular menstrual cycles, no current use of hormonal contraception, and no acts of UPI more than 120 hours (both studies) or less than 48 hours (for Study 509 only) before requesting EC. There was no restriction on BMI in either study.

The studies' schedules of events were similar and included up to three visits. At the first, screening and treatment occurred. Prior to study drug administration on Day 1, pregnancy status was verified by a high sensitivity urinary pregnancy test ([HSUP] – level of detection of  $\beta$ -hCG to 20 mIU/mL) and a blood sample was taken and stored for potential serum  $\beta$ -hCG pregnancy testing at a later date, if necessary. The study medication, a single dose of ulipristal 30 mg, was administered on Day 1 after all eligibility criteria, including a negative urine pregnancy test, were verified.

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 outcome of the pregnancy test:

- Negative HSUP and resumption of menses: study completion procedures were performed.
- Positive HSUP: a serum  $\beta$ -hCG was performed and if positive, the frozen pre-treatment serum was also analyzed to determine if the subject had been 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  $\beta$ -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.

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.

## 7.2 DEMOGRAPHICS

Table 2 shows the demographics of the randomized populations in each study.

**Table 2 Demographics – Studies 509 and 513 (ITT Population)**

Variable	Study 509 N=1,533	Study 513	
		Ulipristal N=1,104	LNG N=1,117
<b>Age (Years)</b>			
Mean (±SD)	24.4 (6.1)	24.5 (6.1)	24.9 (6.6)
Range	18-50	16-52	16-55
<b>Age Category (%):</b>			
16-17	0	4.0	4.4
18-35	93.5	89.5	88.2
36 and older	6.5	6.5	7.4
<b>Race (%):</b>			
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
<b>Body Mass Index (kg/m<sup>2</sup>)</b>			
Mean (±SD)	25.3 (6.2)	25.3 (5.9)	25.2 (5.7)
Range	16-61	16-70	15-54

Source: Based on NDA 22-474 submission, Study Report for Study 509, Table 2, p 34 and Study Report for Study 513, Table 4, pp 42

### Team Leader Comments

- The demographic features are similar across the two studies, although only Study 513 included women under the age of 18 (a total of 44 < 18 years were randomized to ulipristal and 49 to LNG).
- In the absence of a BMI restriction, some women of very high BMI were enrolled, although even the average BMI of 25 would be considered “overweight.” This likely reflects the US population accurately, where 64% of adult women are considered overweight<sup>1</sup>.

## 7.3 DISPOSITION OF SUBJECTS

A total of 3,754 women were enrolled in the two studies, with a total of 2,637 assigned to receive ulipristal. This constituted the safety population. About 8 to 11% of ulipristal subjects discontinued prematurely for the reasons described in **Error! Reference source not found.**

<sup>1</sup> Flegal KM et al. Prevalence and trends in obesity among US adults, 1999-2008. JAMA. 2010; 303 (3): 235-41

**Table 3 Subject Disposition in Studies 509 and 513 (ITT Population)**

Category	Study 509		Study 513			
	Ulipristal acetate		Ulipristal acetate		Levonorgestrel	
Treated	1,533		1,104		1,117	
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%
<b>Reason for Discontinuation (N, %)</b>						
Lost to follow-up	102	6.7%	48	4.3%	40	3.6%
Other	68	4.4%	36	3.3%	30	2.7%
Withdrew consent	1	<0.1%	5	0.5%	1	0.1%
Adverse event	0	0%	2	0.2%	0	0%

Source: Based on NDA 22-474 submission, Study Report for Study 509, Flow Chart 1, p 30 and Study Report for Study 513, Flow Chart 1, p 39

**Team Leader Comments**

- **With a single dose administration, it is not surprising that the rate of discontinuation is low and primarily attributable to loss to follow-up. Women who did not return for scheduled follow-up visits were considered early discontinuations. This was the situation for the two women in Study 513 who discontinued due to an adverse event (AE).**
- **In Study 509, 105 subjects discontinued following treatment but before follow-up, 34 after follow-up visit 1, and 32 after follow-up visit 2.**
- **In Study 513, of ulipristal subjects, 49 discontinued following treatment but before follow-up, 26 after follow-up visit 1, and 16 after follow-up visit 2.**
- **Therefore, the majority of early terminators were ineligible for the efficacy analysis, as they did not have a known pregnancy status following drug intake.**

**7.4 EFFICACY FINDINGS**

**7.4.1 Assessment of Efficacy**

The primary endpoint was the **pregnancy rate**, defined as the number of pregnancies occurring after taking EC divided by the number of subjects who took EC. For Study 509, the primary efficacy analysis compared the upper bound of the two-sided 95% confidence interval (CI) around the point estimate of the observed pregnancy rate in subjects who took ulipristal between 48 and 120 hours after UPI to the estimated expected pregnancy rate in the absence of EC. For Study 513, 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 of 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 et al<sup>2</sup> using the pooled set of conception probabilities and the estimated cycle day of UPI (described further in Dr. Orleans' review).

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

**Cycle day of UPI =**

$$\text{(Date of UPI - Date of first day of last menstrual period + 1) - (Average length of menstrual cycle - 14)}$$

The Applicant specified that two criteria had to be met for the studies to be considered successful:

- The upper bound of the 95% CI around the point estimate of the observed pregnancy rate in subjects given ulipristal for EC was < the expected pregnancy rate, and
- The upper bound of the 95% CI around the point estimate of the observed pregnancy rate in subjects given ulipristal for EC was < the Applicant's specified "clinical relevance" threshold of 4%.

Secondary endpoints included:

- The prevented fraction of pregnancies
- Trends in efficacy by 24-hour time windows since UPI
- Pregnancy rate for subjects who took ulipristal within 120 hours after UPI (Study 513 only; same analysis as was done in the primary analysis for 0-72 hours)
- Comparison of ulipristal to LNG; if a non-inferiority analysis was significant, ulipristal would be evaluated for superiority to LNG (Study 513 only)

Finally, subgroup analyses by age, race, region and BMI were conducted.

A data safety monitoring board (DSMB) was established, consisting of two gynecologic experts. The DSMB was tasked with reviewing pregnancies and determining whether they were compatible or not compatible with EC failure. This categorization was based on the pre-treatment serum HCG test and gestational age based on ultrasound and other factors as needed. Further details are provided in Dr. Orleans' review. In Study 509, the DSMB considered pregnancies "not compatible" with EC failure if they were documented to have been existent pre-treatment, or if they were conceived outside the calculated fertile window for the woman in question.

**Team Leader Comment**

- **In Study 509, the DSMB excluded three pregnancies from the mITT population (one pre-treatment and two post-treatment). The Division did not agree with exclusion of the purported "pre-treatment" pregnancy, as the data regarding possible time of conception were inconsistent, and therefore were not clear enough to rule out EC failure.**
- **In Study 513, the DSMB excluded three pregnancies from the mITT population (two pre-treatment and one post-treatment). The Division did not agree with exclusion of the post-treatment pregnancy, as the subject's only reported act of UPI was the one for which she took ulipristal.**

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<sup>2</sup> Trussell J, et al. New Estimates of the Effectiveness of the Yuzpe Regimen of Emergency Contraception. Contraception 1998; 57:363-9

The Applicant evaluated a number of analysis populations, including the ITT population, which included all women who received EC; this was also the safety population. The primary efficacy population was considered by the Applicant to be the modified ITT (mITT populating), defined as all ITT subjects who participated for the first time (i.e., repeat enrollment cycles were excluded), had known pregnancy status following drug intake, were aged  $\leq 35$  years, and who did not have a pre-treatment pregnancy or a pregnancy determined by the DSMB as “not compatible” with EC failure.

**Team Leader Comment**

**The Division reviewed the pregnancies excluded from analysis as either pre-treatment or “not compatible” with drug failure. The Division disagreed on only two pregnancies; as noted above; therefore, the efficacy population used by the Division includes one additional pregnancy in each study compared to the Applicant’s mITT. The Division’s population is referred to as the “FDA efficacy population” and results based on this population will be presented in this review.**

Study 513 included a planned interim analysis, to be conducted when 1,200 subjects had been enrolled. An appropriate adjustment was made to the efficacy analyses. The protocol specified that if the upper limit of the 95% CI around the observed pregnancy rate was less than the expected rate and below the clinical relevance threshold of 4%, and ulipristal was shown to be non-inferior to LNG, enrollment would be ended.

The Applicant considered the interim analysis of Study 513 to be the protocol-specified primary analysis, and the Division agreed. However, since the entire study population had been enrolled by the time of the interim analysis, the “final” analysis is also considered informative, and is presented as well.

The Applicant presented a pooled analysis of efficacy also; the Division had indicated prior to NDA submission that efficacy would be evaluated based on each study individually. However, the Division did rely on pooled data to evaluate trends in efficacy by time, and by BMI, as the individual studies were not powered adequately for either of these assessments.

**7.4.1.1 Primary Efficacy Analysis**

The distribution of subjects by 24-hour time windows since UPI is shown for each study in Table 4 and Table 5.

**Table 4 Study 509 – Subjects Presenting for EC by 24-hour Window since UPI**

<b>Time Interval from UPI to Use of EC (hours)</b>	<b>Applicant’s mITT Population N=1,241 n (%)</b>	<b>FDA Efficacy Population N=1,242 n (%)</b>
48 to 72	693 (55.8)	694 (55.9)
73 to 96	390 (31.4)	390 (31.4)
97 to 120	158 (12.7)	158 (12.7)

Source: Table 7, Statistical review by Kate Dwyer, Ph.D., dated July 22, 2010

**Table 5 Study 513 – Subjects Presenting for EC by 24-hour Window since UPI**

Time Interval from UPI to Use of EC (hours)	Ulipristal acetate Subjects N=940 n (%)	Levonorgestrel Subjects N=954 n (%)	Total Subjects N=1,894 n (%)
0-24	312 (33.2)	337 (35.3)	649 (34.3)
25-48	329 (35.0)	319 (33.4)	648 (34.2)
49-72	204 (21.7)	196 (20.5)	400 (21.1)
73-96	63 (6.7)	73 (7.7)	136 (7.2)
97-120	32 (3.4)	29 (3.0)	61 (3.2)

Source: Table 14, Statistical review by Kate Dwyer, Ph.D., dated July 22, 2010

**Team Leader Comment**

- A total of 641 subjects were exposed to ulipristal 0-48 hours after UPI (in Study 513 only). A total of 453 subjects received ulipristal 73-96 hours after UPI, and 190 were dosed 97-120 hours after UPI (in both studies).

Success on the primary efficacy endpoint, observed pregnancy rate compared to the expected rate in the absence of EC and compared to the clinical relevance threshold of 4%, was achieved in both studies (see Table 6, Table 7 and Table 8). In both studies, the upper bound of the 95% confidence interval around the point estimate for the observed pregnancy rate was less than the point estimate of the expected rate and less than 4%.

**Table 6 Study 509 – Pregnancy Rates 48-120 Hours after UPI**

	Applicant's mITT Population N=1,241	FDA Efficacy Population N=1,242
Estimated Expected Pregnancies per Trussell (n)	69	69
Estimated Expected Pregnancy Rate (%)	5.53	5.53
Observed Pregnancies (n)	26	27
<b>Observed Pregnancy Rate (%) (95% CI)</b>	<b>2.10 (1.41, 3.10)</b>	<b>2.17 (1.47, 3.19)</b>

Source: Table 8, Statistical review by Kate Dwyer, Ph.D., dated July 22, 2010

**Table 7 Study 513 – Pregnancy Rates 0-72 Hours after UPI (mITT Interim)**

	Ulipristal acetate N=596	Levonorgestrel N=604
Estimated Expected Pregnancies per Trussell (n)	33	36
Estimated Expected pregnancy rate (%)	5.63	5.88
Observed pregnancies (n)	9	17
<b>Observed pregnancy rate (%) (95% CI) *</b>	<b>1.51 (0.62 - 3.32)</b>	<b>2.81 (1.54 - 4.97)</b>

\*95% CI adjusted for interim analysis with the critical value set to  $Z_{0.025}=2.3876$ .

Source: Table 15, Statistical review by Kate Dwyer, Ph.D., dated July 22, 2010

**Table 8 Study 513 – Pregnancy Rates 0-72 Hours after UPI (Final Analysis)**

	Ulipristal acetate		Levonorgestrel
	Applicant's mITT N=843	FDA Efficacy Population N=844	Applicant's mITT and FDA Efficacy Population N=851
Expected Pregnancies per Trussell (n)	46	47	46
Expected pregnancy rate (%)	5.54	5.55	5.43
Observed pregnancies (n)	15	16	22
Observed pregnancy rate (%) (95% CI) *	<b>1.78</b> (1.04, 2.98)	<b>1.90</b> (1.13, 3.12)	<b>2.59</b> (1.68, 3.94)

\*95% CI adjusted for interim analysis with the critical value set to  $Z_{0.025}=2.0056$ .  
 Source: Table 16, Statistical review by Kate Dwyer, Ph.D., dated July 22, 2010

**Team Leader Comments**

- In Study 509, the Division included one pregnancy that had been excluded by the DSMB.
- For the interim analysis in Study 513, the DSMB did not find any pregnancies to be “not compatible” with EC failure. Therefore, the FDA Efficacy population is identical to the mITT Interim population.
- For the supportive, final analysis of Study 513, the Division included one pregnancy that had been excluded by the DSMB.
- Whether based on the Applicant’s mITT or the FDA Efficacy populations, or on the interim or final analysis of Study 513, the success criteria were met in both studies.

**7.4.1.2 Secondary Efficacy Analysis**

The secondary endpoints were also supportive of the efficacy of ulipristal. The prevented fraction of pregnancy for each study is presented in Table 9 and Table 10.

**Table 9 Study 509 – Prevented Fraction of Pregnancies 48-120 Hours after UPI**

Population	Subjects Exposed (N)	Observed Pregnancies (n)	Expected Pregnancies (n)	Prevented Fraction (%; 95% CI)
Applicant’s mITT	1,241	26	69	<b>62.3</b> (41.9, 75.6)
FDA Efficacy Population	1,242	27	69	<b>60.9</b> (40.1, 74.5)

Source: Table 9, Statistical review by Kate Dwyer, Ph.D., dated July 22, 2010

**Table 10 Study 513 – Prevented Fraction of Pregnancies**

Time interval between EC treatment and UPI	Ulipristal acetate		Levonorgestrel
	Applicant's mITT % (95% CI)	FDA Efficacy Population % (95% CI)	Applicant's mITT and FDA Efficacy Population % (95% CI)
0-72 hrs	<b>68.1</b> (45.8, 81.2)	<b>66.0</b> (42.5, 79.9)	52.2 (25.1, 69.5)
0-120 hrs	<b>72.2</b> (52.8, 83.7)	<b>70.4</b> (49.9, 82.5)	52.8 (27.8, 69.2)

\*95% CI adjusted for interim analysis with the critical value set to  $Z_{0.025}=2.0056$ .  
 Source: Table 18, Statistical review by Kate Dwyer, Ph.D., dated July 22, 2010

**Team Leader Comment**

Overall, the prevented fraction for ulipristal ranged from 61% to 70% depending on the timeframe evaluated, using the FDA Efficacy Population. Although this is lower than the prevented fractions for Plan B and Plan B One-Step as reported in the Plan B One-Step labeling (79% and 84%, respectively), in the current comparative study, the prevented fraction demonstrated for LNG 1.5 mg (Plan B One-Step) was about 53%.

The rate of pregnancy by 24-hour windows since UPI is show in Table 11 for the pooled data from both studies.

**Table 11 Pregnancy Rates by 24-Hour Window since UPI (Pooled Data)**

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	5.61	63.9 ( 48.3, 74.7)

Source: Table 21, Statistical review by Kate Dwyer, Ph.D., dated July 22, 2010

**Team Leader Comment**

At every time interval, the upper bound of the 95% CI around the observed pregnancy rate is less than the expected rate and less than 4%, and the prevented fraction of pregnancies exceeds 60%, indicating that ulipristal is efficacious whenever it is taken, within 120 hours after UPI.

The secondary analysis in Study 513 of overall efficacy in the full 120 hours post-UPI also demonstrated success for ulipristal (see Table 12).

**Table 12 Study 513 - Pregnancy Rates 0-120 Hours after UPI**

	Ulipristal acetate		Levonorgestrel
	Applicant's mITT N=939	FDA Efficacy Population N=940	Applicant's mITT and FDA Efficacy Population N=954
Expected Pregnancies per Trussell (n)	54	54	53
Expected pregnancy rate (%)	5.72	5.72	5.52
Observed pregnancies (n)	15	16	25
Observed pregnancy rate (%) (95% CI) *	1.60 (0.93, 2.67)	1.70 (1.01, 2.80)	2.62 (1.75, 3.89)

\*95% CI adjusted for interim analysis with the critical value set to  $Z_{0.025}=2.0056$ .

Source: Table 17, Statistical review by Kate Dwyer, Ph.D., dated July 22, 2010

The efficacy of ulipristal in comparison to LNG was evaluated in Study 513. Non-inferiority was to be concluded if the upper bound of the 95% CI around the odds ratio for pregnancy in the ulipristal vs. LNG group was lower than the specified non-inferiority margin of 1.6. If non-inferiority was determined, superiority would be evaluated; superiority would be concluded if the upper bound of the 95% CI around the odds ratio for pregnancy in the ulipristal vs. LNG group was lower than the specified superiority threshold of 1.0.

The upper bound of the 95% CI around the odds ratio was below 1.6, thereby demonstrating that ulipristal is non-inferior to LNG. However, upper bound exceeded the superiority threshold of 1.0, so superiority cannot be concluded (see Table 13).

**Table 13 Study 513 – Odds Ratio for Pregnancy in Ulipristal vs. LNG, 0-72 Hours after UPI**

	Ulipristal acetate N=596	Levonorgestrel N=604
Observed Pregnancy (n)	9	17
Observed Pregnancy Rate (%)	1.51	2.81
<b>Odds Ratio (95% CI)*</b>	<b>0.53 (0.20, 1.44)</b>	

\*95% CI adjusted for interim analysis with the critical value set to  $Z_{0.025}=2.3876$ .  
 Source: Table 20, Statistical review by Kate Dwyer, Ph.D., dated July 22, 2010

**Team Leader Comment**

[REDACTED] (b) (4)

**7.4.1.3 Efficacy in Subgroups**

The FDA statistical reviewer evaluated the effects of race, age, BMI, conception probability and cycle day of intercourse through a logistic regression model. Results for Study 513 are shown in Table 14, showing that cycle day of UPI and BMI have a significant impact on efficacy.

**Table 14 Study 513 - Results of Logistic Regression Model (FDA Efficacy Population)**

Effect	Wald Chi-Square	Degree of Freedom	Pr > Chi-Square
Treatment	0.89	1	0.3459
Cycle Day of Intercourse	11.96	1	0.0005
BMI Group	16.69	2	0.0002

Source: Table 22, Statistical review by Kate Dwyer, Ph.D., dated July 22, 2010

**Team Leader Comments**

- The effect of race could not be definitively evaluated due to the small numbers of minority/ethnic women studied.
- There was no apparent effect of age on efficacy, although the subgroups of women < 18 and > 35 years old were small.
- Ulipristal was efficacious in both the US and European populations enrolled in Study 513, although the observed pregnancy rate in Europe was lower than that in the US.

The effect of BMI was further explored in each study and in pooled data from both studies. The results contrasting efficacy in women with BMI  $\leq 30$  mg/m<sup>2</sup> and with BMI  $> 30$  mg/m<sup>2</sup> are displayed in Table 15.

**Table 15 Efficacy by BMI in Studies 509, 513 and Pooled Data**

Study / Time Window	BMI Subgroup (kg/m <sup>2</sup> )	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 (%)
HRA2914-509*	BMI $\leq 30$	21 / 1035	2.03 (1.30, 3.13)	5.76	NA		
	BMI $> 30$	6 / 207	2.90 (1.15, 5.45)	4.37			
	48 – 120 Hour Total	27 / 1242	2.17 (1.47, 3.19)	5.25			
HRA2914-513**	BMI $\leq 30$	11 / 717	1.53 (0.81, 2.80)	5.71	12 / 716	1.68 (0.91, 2.98)	5.63
	BMI $> 30$	5 / 127	3.94 (1.41, 5.29)	4.61	10 / 135	2.41 (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 $\leq 30$	32 / 1832	1.75 (1.22, 2.48)	5.83	14 / 800	1.75 (1.00, 2.98)	5.71
	BMI $> 30$	11 / 350	3.14 (1.67, 5.38)	4.48	11 / 154	1.14 (3.85, 12.6)	4.53
	0 – 120 Hour Total	43 / 2182	1.97 (1.45, 2.67)	5.45	5.61	2.62 (1.75, 3.89)	5.52

\* The analysis population for study HRA2914-509 is the FDA efficacy population.

\*\* The analysis population for study HRA2914-513 is the Final FDA efficacy population.

Source: Table 27, Statistical review by Kate Dwyer, Ph.D., dated July 22, 2010

**Team Leader Comments**

- In both studies and the pooled data, the upper bound around the observed pregnancy rate for ulipristal-treated women exceeded the expected pregnancy rate for the subgroup of women with BMI above 30 mg/m<sup>2</sup>, indicating that efficacy may be attenuated in heavier women.
- In the LNG arm of Study 513, looking at efficacy in both the 0-72 and 0-120 hour time windows, the upper bound exceeded the expected pregnancy rate and the point estimate of the observed rate also exceeded the expected rate. This suggests that the impact of BMI on efficacy may be even more pronounced if LNG is used for EC. However, the lower bounds of the observed rates were below the expected rates, so the diminution of efficacy is not statistically significant.
- The data clearly suggest that heavier women may experience lower efficacy with EC regardless of the product used. However, in the absence of any alternative that has been shown to have robust efficacy regardless of BMI, heavier women should not be discouraged from using EC.
- The impact of BMI on efficacy should be described in labeling in a balanced manner that does not imply superiority for either ulipristal or LNG.

### **Statistician's Conclusion**

The statistical reviewer, Kate Dwyer, Ph.D., confirmed the Applicant's primary efficacy findings. As noted, the efficacy population used by FDA was not identical to that used by the Applicant, because the clinical reviewers did not agree with all decision made by the DSMB as to which pregnancies were "not compatible" with EC failure. However, even with a slightly greater number of pregnancies, the overall conclusions reached in the analysis were unchanged. Dr. Dwyer noted that both studies had reasonable rates of early discontinuation, and recruited an adequate number of subjects for the anticipated effect size, to allow at least 80% power in evaluating the efficacy of ulipristal.

Dr. Dwyer reached the following conclusions in her review of July 22, 2010:

*From a statistical perspective, the data provided from the two studies demonstrated that treatment with Ulipristal 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 also observed using different analysis populations (e.g., mITT, mITT2, PP and ITT completers). 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 BNMI > 30 kg/m<sup>3</sup>.*

### **7.4.2 Overall Assessment of Efficacy**

The pivotal phase 3 studies conducted by the Applicant provided robust confirmation of the efficacy of ulipristal for EC when used within 120 hours of UPI. Both studies met the dual criteria for success, and secondary endpoints were also supportive of efficacy. Ulipristal was shown to be efficacious in each of the five 24-hour intervals in the 0-120 hour post-UPI treatment window. Ulipristal was also shown to be statistically non-inferior to LNG in the comparator study. Of various subgroups evaluated, the only variable that appears to impact efficacy is BMI; higher BMI (> 30 mg/m<sup>2</sup>) appears to be associated with a reduction in efficacy for EC in general, as this effect was demonstrated for both ulipristal and LNG. Based on the data from these studies, there are no grounds for recommending preferential use of either product by women of higher BMI.

## **8. Safety**

The ulipristal safety database includes data from nine phase 1 PK/PD studies, two phase 2 studies, and two phase 3 studies (see Table 16). The phase 2 and 3 studies investigated ulipristal for the indication of EC. All studies, with the exception of one phase 1 study, used single doses of ulipristal. Four of the phase 1 studies and both phase 3 studies used the to-be-marketed formulation (30 mg of micronized ulipristal). The studies providing the majority of safety data in this application are phase 3 studies 509 and 513.

Overall, 4,789 subjects received ulipristal and were studied for safety in the clinical development program. Among these subjects, 2,764 (57.9%) received the to-be-marketed 30 mg ulipristal tablet. Four repeat enrollers were reported in the phase 2 studies. In the phase 3

studies, 84 subjects enrolled more than once (75 enrolled twice and 9 others enrolled three times). Because subjects were re-randomized, only 82 subjects took ulipristal more than once (73 received ulipristal twice and 9 received it three times). Safety analyses were performed on the ITT population (all subjects who received treatment with ulipristal).

**Table 16 Overall Exposure – Safety Populations of Phase 1, 2, and 3 Studies for Ulipristal**

Study	Treatment dose, route, regimen of Ulipristal Acetate	Subjects evaluated for safety	Study duration	Overall median of exposure
<b>Phase 1 Trials (9)</b>				
HRA2914-501	-10 mg non-micronized and micronized capsule; -10 mg micronized tablet	10	Single dose	-
HRA2914-503	-Up to 200 mg non-micronized	31	Single dose	-
HRA2914-504	-30 mg micronized tablet	20	Single dose	-
HRA2914-505	-Up to 100 mg non-micronized	32	Single dose	-
HRA2914-506	-Up to 100 mg non-micronized	41	Single dose	-
HRA2914-510	-2.5 mg micronized tablet -5 mg micronized tablet -10 mg micronized tablet	12 12 11	84 days	83.6 days
<b>HRA2914-511</b>	-30 mg micronized tablet*	35	Single dose	-
<b>HRA2914-512</b>	-30 mg micronized tablet*	19	Single dose	-
<b>HRA2914-516</b>	-30 mg micronized tablet*	53	Single dose	-
<b>Phase 2 Trials (2)</b>				
HRA2914-507	-50 mg non-micronized/Placebo -0.75 mg x 2 LNG	832 840	Two doses 12 hours apart	-
HRA2914-508	-10 mg micronized capsule -10 mg non-micronized capsule -50 mg non-micronized capsule	399 214 413	Single dose	-
<b>Phase 3 Trials (2)</b>				
<b>HRA2914-509</b>	-30 mg micronized tablet*	1,533	Single dose	-
<b>HRA2914-513</b>	-30 mg micronized tablet* or -1.5 mg LNG	1,104 1,117	Single dose	-

\*To-be-marketed dose of ulipristal.

Source: NDA 22-474 submission, Summary of Clinical Safety, Adapted from Table 2.7.4-1, p 9

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.

Safety evaluations included laboratory monitoring in a subset of 112 subjects from Study 509, pregnancy testing and adverse event reporting.

### 8.1 Deaths and Serious Adverse Events

There were no deaths in the clinical development program.

There were four serious adverse events (SAEs) in phase 1 studies, including “bacterial pneumopathy,” abdominal pain and fever, Graves disease and pilonidal cyst. None were

considered drug-related. In the phase 2 studies, two SAEs were reported by ulipristal subjects, a kidney infection two months post-treatment and pelvic inflammatory disease one month post-treatment. Neither was considered drug-related. Four SAEs were reported by ulipristal subjects in phase 3:

- Seizure with ecstasy use (Study 509)
- Urinary tract infection, contact lens-related corneal ulcer and dizziness (Study 513)

Only dizziness was considered by the Applicant to be possibly drug-related. LNG subjects in Study 513 reported four SAEs, of hematemesis, molar pregnancy, ruptured ovarian cyst and kidney stones.

A total of two ulipristal subjects discontinued from Study 513 due to an AE. One vomited within 15 minutes of treatment, which was considered by the Applicant to be drug-related. The other experienced a ruptured ovarian cyst 15 days post-treatment, and did not return for further follow-up. The Applicant did not consider this a SAE, nor treatment-related. No subjects in Study 509 discontinued due to an AE.

**Team Leader Comment**

**Ovarian cysts are fairly common when ovulation is inhibited. I would therefore consider that the ruptured ovarian cyst may have been drug-related.**

## 8.2 Other Notable Adverse Events

### Pregnancy

In Study 509, 29 subjects became pregnant, 16 elected to have an induced abortion, 6 reported spontaneous abortions, 6 continued the pregnancy, and one was lost to follow-up. In Study 513, 20 ulipristal subjects and 30 LNG subjects became pregnant, induced abortions were chosen by 14 and 21, respectively; 5 and 4, respectively, miscarried; 0 and 3, respectively, continued the pregnancy; and 1 and 2, respectively, were lost to follow-up, undecided or had a molar pregnancy<sup>3</sup>. Table 17 shows the pooled data for ulipristal and for LNG with regard to pregnancy outcome.

**Table 17 Studies 509 and 513 - Pregnancy Outcome**

Pregnancy outcome	Ulipristal N=2,637	LNG N=1,117
Pregnant	49 (1.9%)	30 (2.7%)
Induced abortion	30 (61%*)	21 (70%*)
Spontaneous abortion	11 (22%*)	4 (13%*)
Continued pregnancy	6 (12%*)	3 (10%*)
Lost/other	2 (4%*)	2 (7%*)

\*Percent based on number of pregnancies, not total N

### **Team Leader Comments**

- **The background rate of spontaneous abortions is about 15-20%, with the vast majority occurring in the first trimester. Neither EC drug was associated with a rate of miscarriage above that expected.**

<sup>3</sup> These data for ulipristal subjects in Study 513 vary by one from that reported in Dr. Orleans' review, because they are based on a June 11, 2010 response to an information request made by the Division, and include one pregnancy in Study 513 that was originally considered to be continuing, but was later miscarried.

- **Because the proportion of spontaneous abortions was slightly greater in the ulipristal arm, the time course of miscarriage was explored to assess whether this might represent an effect of ulipristal, as would be suggested if the miscarriages occurred very early in pregnancy (i.e., peri-implantation). The Applicant was asked to provide data on all pregnancies in phase 3, including outcome and information to allow calculation of the time interval from dosing to outcome. Of 11 spontaneous abortions that occurred in ulipristal subjects, all occurred more than two weeks after dosing with ulipristal and 9 occurred more than three weeks after dosing (range from 22 to 46 days post-dose). This does not suggest that ulipristal is having a post-implantation effect on pregnancies that are conceived following EC failure. Given that the half-life of the drug is 32 hours, the drug is almost completely cleared from the body in about a week, so it is unlikely that residual effects of ulipristal would be observed beyond one week post-dosing. It is possible, however, that a pregnancy might have been lost earlier than the reported outcome date, as some miscarriages are diagnosed only by sonogram, when absence of fetal heart activity is detected.**

#### Effects on bleeding and menstrual cycle

In the phase 3 trials, the mean length of the menstrual cycle following treatment increased by 2.5 days from the baseline mean. About 7% of subjects reported a decrease of at least a week in cycle length and 19% reported an increase of at least a week. Intermenstrual bleeding was reported by 9% of women treated with ulipristal, almost always characterized as spotting. The volume of bleeding with menses was reported as heavy in 16% of women in Study 509 and 34% of ulipristal subjects and 36% of LNG subjects in Study 513. Women who had negative pregnancy tests but had not resumed menses at Follow-up Visit 2 entered the amenorrhea phase. In Study 509, 98 (6.4%) were eligible for this follow-up, and 69% resumed menses in the 60-day period. In Study 513, 43 (3.9%) of ulipristal subjects and 21 (1.9%) of LNG subjects were eligible, and 30 and 15, respectively, resumed menses within 60 days.

#### Ovarian cysts

Ovarian cysts were evaluated by systematic ultrasounds in three phase 1 studies, and were observed in all treatment arms, including placebo. In the repeat dose study, the incidence of ovarian cysts did appear to be dose-proportional, but this was not observed in the single dose studies. In phase 2, cysts were reported with equal frequency in both 10 mg and 50 mg ulipristal subjects. In the phase 3 studies, one subject each in the ulipristal arm and the LNG arm of Study 513 experienced a ruptured ovarian cyst.

### **8.3 Other Adverse Events**

Common adverse events in the phase 2 trials are discussed in Dr. Orleans' review, and are similar to those observed in the phase 3 trials. Table 18 displays common AEs regardless of the Applicant's determination about treatment-relatedness.

**Table 18 Studies 509 and 513 - Common Adverse Events (≥ 2% of Subjects (ITT Population))**

Preferred Term	Study	Study		Pooled Data
	HRA2914-509	HRA2914-513		(Studies 509+513)
	Ulipristal (N=1,533) n (%)	Ulipristal (N=1,104) n (%)	Levonorgestrel (N=1,117) n (%)	Ulipristal (N=2,637) n (%)
At least one AE	876 (61)	597 (54)	626 (56)	1473 (56)
Headache	269 (18)	213 (19)	211 (19)	482 (18)
Nausea	187 (12)	141 (13)	126 (11)	328 (12)
Dysmenorrhea	102 (7)	142 (13)	160 (14)	244 (9)
Abdominal pain + upper abdominal pain	229 (15)	93 (8)	121 (11)	322 (12)
Fatigue	86 (6)	61 (6)	44 (4)	147 (6)
Dizziness	83 (5)	57 (5)	55 (5)	149 (5)
Nasopharyngitis	41 (3)	31 (3)	32 (3)	72(3)
Back pain	37 (2)	35 (3)	27 (2)	72 (3)
Pelvic pain	59 (4)	0	0	59 (2)
Abdominal distension	32 (2)	17 (2)	14 (1)	49 (2)

Source: NDA 22-474 submission, Summary of Clinical Safety, adapted from Table 2.7.4-5, p 19

**Team Leader Comments**

- **Nasopharyngitis is not likely to be drug-related; the other AEs may plausibly be related to EC intake.**
- **The common AE profile is very similar between ulipristal and LNG.**

Laboratory data were obtained only in a subset of subjects in Study 509, and did not provide any signal of concern. No decrease in mean hemoglobin was noted, and very few subjects had baseline to end-of-study shifts from normal to high in any laboratory parameter.

**Team Leader Comment**

**Although the phase 3 laboratory database is small, it is probably more relevant that 35 women who received lower doses of ulipristal daily for 12 weeks had baseline and end-of-treatment labs (see next section).**

**8.4 Safety in Special Populations**

**Multiple dose subjects in phase 1**

The phase 1 trials' safety data are discussed in Dr. Orleans' review, and did not reveal any findings of concern. In the single study evaluating long-term (12 weeks) use of lower doses of ulipristal, a total of 35 women received doses of 2.5 mg, 5 mg or 10 mg of micronized ulipristal. Treatment-emergent AEs were generally not dose-proportional, with the exception of ovarian cysts and abdominal pain. AEs that occurred in at least 10% of subjects in any treatment arm are shown in Table 19.

**Table 19 AEs Occurring in > 10% of Subjects in Study 510 (12 weeks)**

	2.5 mg (n=12) n (%)	5 mg (n=12) n (%)	10 mg (n=11) n (%)	Placebo (n=11) n (%)
Ovarian Cyst (>20mm)	2 (16.6)	6 (50.0)	9 (81.8)	1 (9.1)
Dysmenorrhœa	3 (25.0)	2 (16.7)	1 (9.1)	2 (18.2)
Uterine polyp	1 (8.3)	2 (16.7)	1 (9.1)	1 (9.1)
Pelvic pain	1 (8.3)	2 (16.7)	1 (9.1)	
Breast pain	2 (16.7)	1 (8.3)	1 (9.1)	
Uterine Cyst		2 (16.7)		
Headache	6 (50.0)	5 (41.7)	4 (36.4)	2 (18.2)
Abdominal pain	1 (8.3)	2 (16.7)	2 (18.2)	1 (9.1)
Lower abdominal pain				2 (18.2)
Nausea		2 (16.7)		1 (9.1)
Vomiting	2 (16.7)		1 (9.1)	
Constipation	2 (16.7)			
Acnea		3 (25.0)	2 (18.2)	

Source: NDA 22-474 submission, Study Report for Study 510, Table T-12, p 59

**Team Leader Comment**

**Ovarian cysts are not unexpected with prolonged use of a product that inhibits ovulation. The cysts spontaneously resolved during treatment or post-treatment in all but one subject.**

Two SAEs occurred in this study (included among the four noted earlier in this review in phase 1 studies), hyperthyroidism (Graves disease) in a subject on 5 mg, who had abnormal thyroid tests at baseline, and abdominal pain considered to be an inflammatory syndrome that resulted in study discontinuation in a subject on 10 mg. Neither was considered drug-related.

Laboratory values, including liver function, electrolytes, lipids, glucose and cortisol, did not change markedly from baseline to end of treatment.

**Recurrent users in phase 2 or 3**

A relatively small number of recurrent users enrolled in phase 2 and phase 3 studies, none used ulipristal more than three times. There was no increase in the occurrence or seriousness of AEs in this group, and their laboratory parameters (in Study 509) did not show marked changes from baseline. No pregnancy occurred in a repeat enroller (513). There were also no changes in duration or volume of uterine bleeding during menses or during inter-cyclic bleeding.

**8.5 Postmarketing Safety Findings**

Ulipristal has been marketed abroad only for about one year, and the postmarketing data available from the EU were reported in the safety updates discussed in the next section.

## 8.6 Safety Update

The Applicant submitted a safety update on February 11, 2010, which included a Periodic Safety Update Report (PSUR) for the period May 15, 2009 through November 15, 2009, and line listings for data up to February 10, 2010. This PSUR covered the first six-month period of marketing for EllaOne in Europe. During this period, market exposure was estimated at 9,500 women, one safety report of a nonserious, listed event was received, and no significant safety-related actions by regulatory authorities were reported. The CHMP was considering a label change based on data obtained in Studies 511 and 513 (relating to mechanism of action and clinical efficacy, respectively). Based on the accumulated safety data, the Marketing Authorization Holder no longer considered increased blood pressure or amenorrhea as potential risks.

### Team Leader Comment

**The labeling change noted in this safety update was incorporated into the European labeling, and included removal of the endometrial effects described previously described under the mechanism of action section, based on the findings of Study 511.**

At the time of the Advisory Committee meeting, the Applicant provided updated information on pregnancies in the clinical trials and from postmarketing reports. Of 92 total pregnancies in ulipristal-treated women in phase 3, 82 had outcome data; of these, 60 (73%) had electively terminated, 15 (18%) experienced spontaneous loss, and 7 (9%) resulted in live births. There were no ectopic pregnancies. Of the seven live births, five were reportedly normal infants, one had optic nerve hypoplasia and developmental delay, and one had an unknown outcome.

In postmarketing reporting from Europe, 21 pregnancies had been reported, with 14 ongoing and apparently normal. Two had been electively terminated, one miscarried, and four lost to follow-up.

## 8.7 Overall Assessment of Safety Findings

The safety profile of ulipristal administered in a single dose was well-characterized, with over 2,764 women receiving the to-be-marketed dose of 30 mg. In addition, a small number of women (88) who received ulipristal two or three times in different cycles during the clinical trials did not show any alteration of concern in the overall safety profile. Women in a phase 1 study who received a 2.5 mg, 5 mg or 10 mg daily dose over 12 weeks also did not experience laboratory alterations or adverse events of concern. There were no deaths and very few SAEs or discontinuations related to AEs in the clinical trials. Common AEs were those frequently observed with hormonal contraception products, and very similar to those seen in the comparator arm of women who used LNG EC. The alterations in menstrual cycle and bleeding volume noted in the phase 3 trials were well-tolerated, and do not represent a safety signal. The outcomes of pregnancies conceived despite use of EC were similar among ulipristal- and LNG-treated women, and there does not appear to be a signal of increased early pregnancy loss associated with ulipristal. With only seven live births reported following use of ulipristal (including one with an abnormal outcome), it cannot be determined whether there is an elevated risk of congenital anomalies following exposure to ulipristal of an undetected pregnancy or a pregnancy resulting from EC failure.

## 9. Advisory Committee Meeting

A meeting of the Advisory Committee for Reproductive Health Drugs (ACRHD) was held to discuss this NME product on June 17, 2010. The questions posed to the ACRHD and the votes are listed below.

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*

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*

3. **Should product labeling include any recommendations on use in specific subpopulations (e.g., women with a BMI > 30 kg/m<sup>2</sup> 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*

Some Committee members concluded that patients and providers should be informed that efficacy may be lower in women with BMI > 30 mg/m<sup>2</sup>, but other members were concerned that providing information in labeling about relative contraceptive efficacy might discourage heavier 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 differentiate this product from other products in which there is also little efficacy data for use in this population.

### Team Leader Comment

The labeling will provide balanced information relative to the impact of higher BMI on efficacy as observed with ulipristal in both studies and with the LNG arm in Study 513. No recommendation discouraging use of any emergency contraception product by heavier women will be made.

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*

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:**

- 1) **Expansion to the US of the planned European study to obtain clinical follow-up data on pregnancy outcomes from women exposed to ulipristal**
- 2) **Retrospective survey of hospitals and providers to evaluate complications of pregnancy loss following the use of ulipristal (e.g., bleeding, infection)**

Some Committee members were opposed to requiring pregnancy testing prior to prescribing, noting that healthcare providers know how to rule out pregnancy, and that pregnancy testing would be used in practice when needed.

Committee members were concerned about the ability of pharmacovigilance (i.e., spontaneous reporting) to provide valid data about pregnancy outcomes, but were in agreement with expanding the planned European study to the US; this study will prospectively follow women who have received ulipristal.

Committee members were also in favor of labeling that would restrict use by lactating women, as data on excretion of ulipristal into breast milk are not available.

## 10. Pediatrics

The Applicant requested a waiver of pediatric studies, on the grounds that the indication is only relevant in postmenarcheal women, and that the FDA has previously endorsed the extrapolation of efficacy from adult to adolescent (i.e., postmenarcheal) populations. The Pediatric Review Committee (PeRC) granted a partial waiver for ages 0 to 11 years (i.e., premenarcheal patients), because the risk of pregnancy does not exist in this population. The remainder of the Pediatric Research Equity Act (PREA) requirement has been fulfilled by extrapolation from studies on adult women (and on the approximately 40 women aged 16 to 18 included in Study 513).

Although no additional studies were required under PREA, the Applicant had proposed to do a study of use in adolescents to address EMA needs for additional data on adolescent use. The Division agreed that, as this is an NME, it is warranted to require that additional data pertaining to use by adolescents. While safety and efficacy are expected to be the same as that demonstrated in adult women, the Division is particularly interested in whether use of ulipristal results in alterations in the menstrual cycle that differ from those observed in adult women. This is a theoretical possibility because the hypothalamic-pituitary-ovarian axis is more labile in adolescents<sup>4</sup> and may be more vulnerable to disruption by a hormone modulator.

## 11. Other Relevant Regulatory Issues

The Applicant submitted financial disclosure information for investigators who participated in Studies 507, 508, 509 and 513. None reported having a financial arrangement with the Applicant, a proprietary interest in the product, or significant equity in the Applicant.

Site inspections by the Division of Scientific Investigation (DSI) were requested for two investigators, both of whom oversaw multiple study sites, and for the Applicant's conduct with respect to Studies 509 and 513 (standard for NME products). The two investigators were chosen because of the large number of subjects enrolled over their sites. Dr. Ginde enrolled a

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<sup>4</sup> Apter, D. Development of the Hypothalamic-Pituitary-Ovarian Axis. *Ann NY Acad Sci.* 1997; 816: 9-21

total of 217 subjects over two sites who completed Study 509, and the DSI inspection resulted in a No Action Indicated (NAI) letter, stating to DRUP that

*No regulatory violations were noted.*

*The study appears to have been conducted adequately, and the data generated by these sites appear acceptable in support of the respective indication.*

Dr. Casale enrolled a total of 269 subjects over two sites who completed Study 513, and the DSI inspection resulted in a Voluntary Action Indicated (VAI) letter, because a total of five subjects were enrolled despite violations of entry criteria, including two who had intercourse more than 120 hours prior to requesting EC, and because a total of nine subjects were enrolled in the wrong time window, due to an error in calculating the time window (within 72 hours or between 72-120 hours after UPI). However, the Applicant noted that these subjects were excluded from the Per Protocol analysis. The overall conclusion for each site was that

*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.*

*The study appears to have been conducted adequately, and the data generated by these sites appear acceptable in support of the respective indication.*

**Team Leader Comment**

**The FDA statistical reviewer calculated time windows since UPI independently, and the efficacy data did not change when these subjects were correctly classified.**

DSI's note to DRUP concerning the Applicant inspection noted that:

*No significant observations of noncompliance were observed.*

*The studies appear to have been conducted adequately, and the data submitted by the sponsor may be used in support of the respective indication.*

## 12. Labeling

The proprietary name **ella** was approved by the Division of Medication Error Prevention and Analysis (DMEPA).

The label was submitted in the format prescribed by the Physician Labeling Rule (PLR), and initially did not include patient labeling. Upon request by DRUP, the Applicant submitted a Patient Package insert. Review of this label was informed in part by the internal updated draft Guidance for oral contraceptive (OC) labeling, as well as by the approved PLR labels for the LNG EC products Plan B and Plan B One-Step. Consultative reviews were provided by the Division of Drug Marketing, Advertising and Communication (DDMAC), the Study Endpoints and Label Development (SEALD) team, and the Division of Risk Management (DRISK), and their comments were incorporated into the label as appropriate.

The major issues addressed in labeling negotiations with the Applicant included:

- Inclusion in Warnings and Precautions section of the need to rule out pregnancy prior to prescribing ulipristal, with use of pregnancy testing if pregnancy could not be excluded by history and/or physical exam

- Description of the likely mechanism of action, including effects on the endometrium, in the Clinical Pharmacology section
- Discussion of the apparent impact of high BMI on the EC efficacy of both ulipristal and LNG

Agreement with the Applicant on labeling was reached on August 12, 2010.

## 13. Recommendations/Risk Benefit Assessment

### 13.1 Recommended Regulatory Action

I recommend that ulipristal acetate be approved for the indication “prevention of pregnancy following unprotected intercourse or known or suspected contraceptive failure,” with the drug to be taken within 120 hours after the act of intercourse of concern.

### 13.2 Risk Benefit Assessment

Ulipristal demonstrated compelling efficacy as an emergency contraceptive in two trials, and according to two co-primary efficacy endpoints and several secondary endpoints. Ulipristal was shown to be non-inferior to the approved emergency contraceptive LNG 1.5 mg, and showed a non-statistically significant trend toward a greater prevented fraction of pregnancies. Both ulipristal and LNG 1.5 mg showed a trend toward reduced efficacy in women with a BMI > 30 mg/m<sup>2</sup>, and this will be described in labeling. In the absence of an approved emergency contraceptive that appears to have equivalent efficacy in all BMI groups, there is no rationale for cautioning heavy women against the use of either product for EC, but healthcare providers may wish to be particularly vigilant about evaluating for EC failure in heavy women who do not resume menses as anticipated.

The safety profile of ulipristal administered in a single dose was well-characterized, with over 2,764 women receiving the to-be-marketed dose of 30 mg. In addition, a small number of women (88) who received ulipristal two or three times in different cycles during the clinical trials did not show any alterations of concern in the overall safety profile. Women in a phase 1 study who received a 2.5 mg, 5 mg or 10 mg daily dose over 12 weeks also did not experience laboratory alterations or adverse events of concern. Finally, early postmarketing data from Europe, where ulipristal has been marketed for about a year, does not indicate any unexpected safety signals.

Issues that could not be clearly elucidated in preapproval studies include the potential fetal risk if the pregnancy is not prevented and conception occurs in a timeframe that allows exposure to ulipristal, and the potential maternal risk if an ongoing pregnancy is exposed to ulipristal, such as pregnancy loss with incomplete evacuation of the uterus, which could then result in bleeding, infection or need for surgical management. While the incidence of such events is anticipated to be too low to permit characterization in a preapproval study of several thousand women, a post-marketing study will be required to obtain pregnancy outcome data on women who are treated with ulipristal in the US and Europe.

Overall, the use of ulipristal for the prevention of pregnancy following UPI or a known or suspected contraceptive failure has a favorable risk/benefit profile.

### **13.3 Recommendation for Postmarketing Risk Evaluation and Management Strategies**

No postmarketing risk management activities beyond labeling and the postmarketing requirements and commitments described below are recommended.

### **13.4 Recommendation for Other Postmarketing Requirements and Commitments**

The following postmarketing studies should be required as a condition of approval:

1. A prospective, observational pregnancy outcome study to include fetal and neonatal outcomes and maternal pregnancy complications following a pregnancy exposed to ulipristal (e.g., in case of inadvertent administration to a woman with an unrecognized early pregnancy, or in case of emergency contraceptive failure). The Applicant has already proposed to conduct such a study in Europe as part of the EMA approval requirements (at least 1,000 prescribers will be recruited to participate within a year in Europe), and should be required to add a US component to the study.
2. A case-control study of maternal complications of pregnancy loss (such as hemorrhage, infection, need for surgical intervention) following exposure to ulipristal during pregnancy; this study would be conducted if a signal of concern regarding pregnancy loss complications is noted in the pregnancy outcome study.
3. A PK study of the potential for ulipristal excretion into breast milk; the Applicant has already proposed to conduct such a study in Chile as part of the EMA approval requirements.
4. An observational study of use in adolescents, with particular attention to the possibility of alterations of the menstrual cycle following use; the Applicant has already proposed to conduct such a study in Europe as part of the EMA approval requirements, and should be required to add a US component to the study, as well as to ensure that at least 50 of the completing subjects worldwide are under the age of 16.

In addition, the Applicant should agree to a postmarketing commitment to conduct an *in vivo* drug-drug interaction study to evaluate the impact of a CYP3A4 inducer on the pharmacokinetics of ulipristal.

In a letter dated August 12, 2010, the Applicant agreed to the specified postmarketing requirements and commitment, and agreed to the following timetables:

1. Pregnancy outcome study:

Final Protocol Submission:	February 13, 2011
Study Completion Date:	December 31, 2013
Final Report Submission:	June 30, 2014
2. Case-control study:

Final Protocol Submission:	February 13, 2011
Study Completion Date:	December 31, 2014
Final Report Submission:	June 30, 2015

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3. Lactation study:
  - Final Protocol Submission: October 13, 2010
  - Study Completion Date: October 13, 2011
  - Final Report Submission: April 30, 2012
4. Adolescent study:
  - Final Protocol Submission: February 13, 2011
  - Study Completion Date: April 30, 2012
  - Final Report Submission: October 30, 2012
5. CYP3A4 inducer study:
  - Final Protocol Submission: February 13, 2011
  - Study/Trial Completion: February 13, 2013
  - Final Report Submission: August 13, 2013

### **13.5 Recommended Comments to Applicant**

None

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

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/s/

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LISA M SOULE  
08/13/2010

SCOTT E MONROE  
08/13/2010

I concur with the recommendation of Dr. Soule that NDA 022474 be approved.