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STATISTICAL REVIEW(S)



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STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number: 22-474 / N000

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Indication(s): Emergency contraception within 120 hours (b) (4) of unprotected intercourse or contraceptive failure

Applicant: Ulipristal Acetate

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List of Abbreviations and Definitions

| | |
|--------------|---|
| BMI | Body mass index |
| CI | Confidence interval |
| DSMB | Data Safety Monitoring Board |
| EC | Emergency contraception |
| FDA | Food and Drug Administration |
| HSUP test | High sensitivity urine pregnancy test |
| β -hCG | Beta human chorionic gonadotropin |
| ICF | informed consent form |
| ITT | Intent-To-Treat |
| IUD | Intra-Uterine Device |
| mITT | Modified Intent-To-Treat |
| NDA | New Drug Application |
| OR | Odds ratio |
| SD | Standard deviation |
| UPI | Unprotected intercourse or a known or suspected contraceptive failure |
| US | United States |

1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

Data support the efficacy of Ulipristal acetate 30 mg as an emergency contraception (EC) within 120 hours after unprotected intercourse (UPI). The observed pregnancy rates for treatment with Ulipristal administered within 120 hours after UPI in two studies were statistically lower than the expected rates in the absence of EC and lower than the clinical relevance threshold of 4%.

1.2 Brief Overview of Clinical Studies

Two phase 3 studies were conducted to support the efficacy and safety of Ulipristal. Study HRA2914-509 was a prospective, open-label, single arm, multicenter study conducted in 40 centers in the United States. In this study, subjects were treated with a single dose of Ulipristal acetate 30 mg, administered between 48 and 120 hours after UPI.

Study HRA2914-513 was a prospective, multicenter, randomized, single-blind, parallel group, comparative trial, conducted both in the United States and in Europe. Subjects were treated with a single dose of either Ulipristal acetate 30 mg or levonorgestrel 1.5 mg between 0 and 120 hours after UPI. An overview of the two studies is provided in Table 1.

Table 1: Brief Summary of Phase III Clinical Studies for Ella®

| | | | | | |
|---|---|--|--------------------------|----------------------|------------------------------|
| HRA2914-509 (40 / U.S.) Nov. 2006 to Mar. 2008 | Women 18 or greater years of age, with regular cycle length (24 to 35 days) presenting for emergency contraception between 48 and 120 hours of UPI | pregnancy rate, calculated as the number of pregnancies after the intake of EC over the total number of subjects administered EC | Ulipristal acetate 30 mg | 1,533 (1,241) | P, OL, MC |
| | | | Total | 1,533 (1,241) | |
| HRA2914-513 (10 / UK, 1 / Ireland, 24 / U.S.) Apr. 2007 to Apr 2009 | Women 16 or greater years of age, with regular cycle length (24 to 35 days) presenting for emergency contraception within 120 hours of UPI ² | | Ulipristal acetate 30 mg | 1,104 (941) | P, R, PG, SB, MC |
| | | | Levonorgestrel 1.5 mg | 1,117 (958) | |
| | | | Total | 2,221 (1,899) | |

¹ P = Prospective, OL = Open-Label, R = Randomized, PG = Parallel Groups, SB = Single-blind, MC = Multicenter

² Because the active control was levonorgestrel, the time frame for the primary efficacy analysis covered the time period of 0 to 72 hours after UPI (the approved window for use of levonorgestrel for EC)

1.3 Statistical Issues and Findings

This review noted one issue regarding the applicant's exclusion of few pregnancies from the efficacy analysis population because the Data Safety Monitoring Board (DSMB) determined that these pregnancies were "not compatible" with EC failure. However, the Division reviewed all such cases and determined that these additional pregnancies should be included in the primary efficacy population. Therefore, this review is based on FDA Efficacy Population that included these additional pregnancies.

The results using both Applicant's mITT (modified-intent-treat) and FDA Efficacy Populations showed that the observed pregnancy rates were statistically significantly lower than the expected pregnancy rate in the absence of EC and met the clinical relevance threshold of < 4%, the success criteria pre-specified in the protocol for both studies. Results of the secondary efficacy analyses supported the findings of the primary efficacy analyses. The results were also consistent across subgroups of age, race and region. The efficacy of ulipristal remained consistent regardless of the time interval between UPI and treatment with ulipristal up to 120 hours after UPI. However, the effectiveness of Ulipristal (as well as levonorgestrel for EC) appeared to be attenuated in subjects with a BMI > 30 kg/m². Both studies had reasonable dropout rates and recruited an adequate number of subjects for the planned effect size to assess the efficacy of the doses under investigation with at least 80% power.

2. INTRODUCTION

Ulipristal (CDB-2914), a new molecular entity, is a selective progesterone receptor modulator that reversibly blocks the progesterone receptors in target tissues. Ulipristal was initially developed at the US National Institutes of Health. HRA Pharma licensed the molecule in 2000 and took over its development.

The proposed proprietary name for Ulipristal is Ella[®]. Ella[®] is an emergency contraceptive indicated for the prevention of pregnancy following unprotected intercourse or a known or suspected contraceptive failure. Ella is not intended for routine use as a contraceptive.

In support of the proposed indication, the sponsor has submitted two Phase 3 studies – HRA2914-509 (Protocol 2914-005) and HRA2914-513 (Protocol 2914-004).

2.1 Overview of Study HRA2914-509

2.1.1 Objectives

The Primary objective of this study was to demonstrate that the pregnancy rate observed after taking Ulipristal acetate 30 mg, between 48 hours and 120 hours of UPI, was statistically significantly lower than the estimated expected pregnancy rate in the absence of emergency contraception.

The secondary objectives were:

1. To demonstrate that the pregnancy rate observed after taking Ulipristal acetate 30 mg, between 48 hours and 120 hours of UPI, was statistically significantly lower than the Applicant's clinical relevance threshold of 4%;
2. To evaluate the trend in pregnancy rates over time since the time of UPI;
3. To estimate the contraceptive effectiveness (prevented fraction) of Ulipristal acetate 30 mg.

2.1.2 Design and Conduct

Study HRA2914-509 was a single arm, open-label, prospective, multicenter study designed to evaluate the efficacy, safety and tolerability of a single dose of Ulipristal acetate 30 mg as

emergency contraception, administered between 48 and 120 hours after UPI. Because no EC is registered for more than 72 hours after UPI, no active controlled study was performed. The trial was conducted at 40 Planned Parenthood family planning clinics in the United States.

Women 18 or greater years of age, with regular menstrual cycles (between 24 and 35 days), requesting EC between 48 and 120 hours after UPI and who met other inclusion/exclusion criteria were enrolled into the study after they signed the informed consent form (ICF). The schedule of the study events is listed in Table 2. A total of up to three visits were scheduled over the course of the study: treatment visit (Day 1, screening phase and treatment phase) followed by up to two follow-up visits. The study medication of a single dose of Ulipristal acetate 30 mg was administered immediately after all eligibility criteria (including current pregnancy status) were verified. All eligible subjects received the same treatment and were assigned an identification number at the time of enrollment at the clinical site.

Table 2: Schedule of Events: Study HRA2914-509

| Study procedure | Treatment Visit | | Follow-Up Visit 1 | Follow-Up Visit 2 (if required) |
|--|-----------------|-----------------|--------------------------------|----------------------------------|
| | Screening Phase | Treatment Phase | | |
| 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 tests 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) was performed

(Source: Clinical Study HRA291-509 Report; Table 5, page 15-16)

If at the first follow-up visit (5-7 days after expected onset of menses) a subject was determined to be “not pregnant” by the investigator based on a negative High Sensitivity Urinary Pregnancy test (HSUP) and return of menses, or was determined to be pregnant with a positive HSUP confirmed by serum β -hCG (frozen pre-treatment serum was also assayed to verify whether pregnancy was prior to treatment), the subject was considered a study completer and the second follow-up visit (12-14 day after onset of expected menses) was omitted. Any woman who became pregnant was to be followed until the pregnancy outcome was determined.

Subjects kept a home diary calendar from the time of treatment until study completion in which they recorded further intercourse during the cycle, vaginal bleeding, concomitant medications 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.

Sample size was estimated in order to reach at least 80% power for both primary and main secondary efficacy analyses. According to previous international studies on emergency contraception, the expected pregnancy rate in the absence of back-up contraception method is estimated to be 8% according to conception probabilities provided by Trussell et al (1998)¹. A reduction of pregnancy rate by more than half of this pregnancy rate (4%) is considered as clinically meaningful for an EC method for this study by the Applicant.

Assuming a 2.5% pregnancy rate with Ulipristal in the 48-120h interval, 1200 patients were needed to show with 80% power that the upper bound of the 2-sided 95% confidence interval of the pregnancy rate is below 4%. The number of patients are inflated by 10% (n=1320) to adjust for anticipated lost to follow-up.

2.1.3 Analysis Populations

Efficacy was evaluated using the following analysis populations:

1. **Intent-To-Treat (ITT) Population** (=Safety Population) which was consisted of all subjects who received emergency contraception.

The repeat enrollers (enrolled and treated more than once) were included and treated as an independent subject in the analysis.

2. **Intent-To-Treat (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).

¹ Trussell J, Rodriguez G, Ellertson C. New Estimates of the Effectiveness of the Yuzpe Regimen of Emergency Contraception. *Contraception* 1998;57:363–9.

3. **Modified Intent-To-Treat (mITT) Population** consisted of all ITT Completers who met the following criteria:
 - Aged ≤ 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) or as “not compatible” with an EC failure, based on independent evaluation by the Data Safety Monitoring Board (DSMB).
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 all mITT subjects excluding major protocol violators, including intake of hormonal contraception or unprotected intercourse after EC intake during study treatment cycle.

The Applicant considered the mITT population as the primary analysis population.

2.1.4 Efficacy Endpoints and Analyses

Primary Efficacy Endpoint

The primary efficacy endpoint was the **pregnancy rate** calculated as the number of pregnancies after the intake of emergency contraception divided by the total number of subjects having received emergency contraception.

The expected pregnancy rate was estimated according to a method provided by Trussell et al (1998) and using pooled recognizable set of conception probabilities. Furthermore, in the event that a woman has had multiple acts of UPI before treatment during the cycle, the conception probability taken into account was that of the act of intercourse carrying the greatest conception probability. The intercourse was determined to be unprotected if contraception not used, or used but failed for some reasons.

Pregnancy status (yes/no) determination:

- 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 pooled recognizable set of conception probabilities estimated by Trussell et al (1998)² is listed in Table 3.

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

$$\text{Cycle day of intercourse} = (\text{Date of unprotected intercourse} - \text{Date of first day of last menstrual period} + 1) - (\text{Average length of menstrual cycle} - 14).$$

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

The estimated expected pregnancy rate for the study population using the conception probabilities was calculated by the following formula. The subjects were clustered by their cycle days of intercourse into 9 groups (< -5, -5, -4, etc.).

$$\text{Estimated expected pregnancy rate} = \frac{\sum_{k=1}^9 N_k P_k}{\sum_{k=1}^9 N_k}$$

Where N_k is the number of subjects whose cycle day of intercourse in the k^{th} group, and P_k is the conception probability of the k^{th} group.

The 95% CI of the observed pregnancy rate was estimated using the Agresti-Coull interval

estimation for a binomial parameter, which is $\tilde{p} \pm z_{\alpha/2} \sqrt{\frac{\tilde{p}\tilde{q}}{\tilde{n}}}$, where $\tilde{p} = \frac{n + z_{\alpha/2}^2 / 2}{N + z_{\alpha/2}^2}$, $\tilde{q} = 1 - \tilde{p}$,

$\tilde{n} = N + z_{\alpha/2}^2$, and n = number of pregnancy and N = total number of subjects in the study

population. The observed pregnancy rate is $p = \frac{n}{N}$.

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 between 48 and 120 hours after UPI to the estimated expected pregnancy rate in the absence of EC. Efficacy was demonstrated if the observed pregnancy rate was declared statistically significantly lower than the estimated expected pregnancy rate and the upper bound of the 2-sided 95% confidence interval of the point estimate was also below the estimated expected pregnancy rate.

The main secondary endpoint was that Ulipristal was non-inferior to 4% (the Applicant's threshold for clinical relevance), which was determined if the upper limit of the 2-sided 95% confidence interval of the observed pregnancy rate after taking Ulipristal between 24 hours and 120 hours of UPI was lower than 4%.

The clinical trial was considered a success if both the primary efficacy analysis and the main secondary analysis (non-inferiority to the clinical relevance threshold of 4%) demonstrate efficacy in the mITT population based on subjects who used Ulipristal between 24 hours and 120 hours after UPI.

Additional Secondary Efficacy Endpoints

1) **Prevented fraction of pregnancies**

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

$$\text{Number of prevented pregnancies} = \text{Number of expected pregnancies} - \text{Number of observed pregnancies}$$

Expected pregnancies and the 95% CI of the prevented fraction were based on conception probabilities by cycle day of intercourse relative to day of ovulation proposed by Trussell et al (1998).

2) **Trend in pregnancy rates**

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.

Missing Data

Missing pregnancy status was treated as not pregnant in the analyses for ITT population; other missing data was not imputed.

Subgroup analyses

No subgroup analyses were planned and conducted by this sponsor.

Interim analysis

An interim analysis was planned using the Lan DeMets' alpha spending function approach, O'Brien-Flemming spending function and an information fraction of $900/1200 = 0.75$. The critical value for the interim analysis was set to $z_{0.025} = 2.3397$ which corresponds to a probability level of 0.0193 and for the final analysis $z_{0.025} = 2.0117$ (instead of 1.96) which corresponds to a nominal alpha of 0.02213 and a cumulated exit probability of 0.05. Therefore 95% confidence intervals presented for primary efficacy analyses were adjusted for interim and final analyses.

2.2 Overview of Study HRA2914-513

2.2.1 Objectives

The primary objective of this study was to demonstrate that the pregnancy rate observed after taking Ulipristal acetate 30 mg within 72 hours of UPI was statistically significantly lower than the estimated expected pregnancy rate in the absence of emergency contraception.

The secondary objectives were:

1. To demonstrate that the pregnancy rate observed after taking Ulipristal acetate 30 mg within 72 hours of UPI was statistically significantly lower than the clinical relevance threshold of 4%;

2. To demonstrate that the pregnancy rate observed after taking Ulipristal acetate 30 mg within 120 hours of UPI was statistically significantly lower than the clinical relevance threshold of 4%;
3. To demonstrate the non-inferiority of Ulipristal acetate 30 mg versus levonorgestrel 1.5 mg as EC within 72 hours of UPI. Should non-inferiority be demonstrated, superiority would be tested;
4. To demonstrate that the pregnancy rate observed after taking Ulipristal acetate 30 mg within 120 hours of UPI was statistically significantly lower than the expected pregnancy rate in the absence of EC;
5. To demonstrate the non-inferiority of Ulipristal acetate 30 mg versus levonorgestrel 1.5 mg as EC within 120 hours of UPI. Should non-inferiority be demonstrated, superiority would be tested;
6. To evaluate the trend in pregnancy rates over time since intercourse after Ulipristal acetate 30 mg or levonorgestrel 1.5 mg;
7. To assess the contraceptive effectiveness (prevented fraction) between treatment groups;

2.2.2 Design and Conduct

HRA2914-513 was a randomized, two-arm parallel groups, single blind (subjects and sponsor blinded and investigator unblinded), multicenter study, conducted in the United States and in Europe. In this study the aimed to evaluate the efficacy of the final dosage form for emergency contraception when used 0 to 120 hours after unprotected intercourse, and to compare the efficacy of Ulipristal acetate 30 with that of the reference treatment, levonorgestrel 1.5 mg single administration. It was performed in 10 centers in UK, one center in Northern Ireland and 24 centers in the US. The sponsor remained blinded to treatment allocation until the database was cleaned and locked for analysis.

Women (aged ≥ 16 years in UK, ≥ 17 years in Northern Ireland and ≥ 18 years in US), with regular menstrual cycles (between 24 and 35 days) and met other the inclusion/exclusion criteria, requesting EC within 72 hours after UPI after they signed the ICF. Women presenting more than 72 hours after intercourse were eligible for inclusion only if they declined the insertion of an Intra-Uterine Device (IUD) for EC or had contraindications to IUD insertion.

The study schedule and conduct were almost identical to that of trial HRA2914-509 (see Section 2.1.2) 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.

An interim analysis was planned to perform on the first 1,200 modified Intent-To-Treat (mITT) subjects who took EC within 72 hours of UPI. In the event that the upper limit of the 95% CI of the observed pregnancy rate was below the estimated expected pregnancy rate and below the clinical relevance threshold of 4%, and that Ulipristal was non-inferior to levonorgestrel (i.e. the odds ratio of pregnancy in the Ulipristal group relative to that in levonorgestrel group is <1.6), the study was to be considered a success and recruitment would be stopped. Otherwise, recruitment was to be continued as planned.

Sample size was estimated in order to reach at least 85% power for the primary efficacy analysis, the main secondary efficacy analysis (non-inferiority to relevance clinical threshold) and the non-inferiority analysis of Ulipristal versus levonorgestrel as EC within 72 hours of UPI.

Assuming a pregnancy rate of 1% and 1.7% with Ulipristal and levonorgestrel, respectively, within 72 hours of UPI, 827 patients per treatment group was randomized in order to demonstrate the non-inferiority of Ulipristal to levonorgestrel using non-inferiority margin of 1% with 2-sided type I error rate of 5% and 85 % power. The sponsor later amended the protocol to change the margin from 1% to 1.6% in odds ratio because the sponsor claimed that non-inferiority margin of 1.6 in odds ratio was equivalent to a non-inferiority margin of 1% in percent point with an assumed pregnancy rate of 1.7% for levonorgestrel. The number of patients were inflated by 10% (n=910) to adjust for anticipated lost to follow-up.

Furthermore, patients requesting EC between 72 and 120 hours were also recruited to assess the efficacy of Ulipristal after 72 hours. Recruitment in this population was estimated to represent 1 out of 10 patients. Therefore, taking into account recruitment in the 72-120 hour interval, 1022 patients per group was randomized for a total of 2044 patients.

2.2.3 Analysis Populations

The analysis populations were defined according to the same criteria as in study HRA2914-509 (see Section 2.1.3), with the addition of the following analysis population:

- **Modified Intent-To-Treat Interim Population (mITT interim)**, which was defined as the first 1200 subjects in the mITT population who enrolled within 72 hours after UPI.

The Applicant considered the mITT population as the primary analysis population.

2.2.4 Efficacy Endpoints and Analyses

Primary Efficacy Endpoint

The primary efficacy endpoint was the pregnancy rate, calculated as the number of pregnancies after the intake of EC divided by the number of subjects having received EC. The objective was to evaluate whether pregnancy rate of Ulipristal was inferior to expected pregnancy rate in the absence of contraception and inferior to the Applicant's clinical relevance threshold of 4%, based on the upper limit of the 95% confidence interval of the observed pregnancy rate.

The estimated expected pregnancy rate was calculated according to the method of Trussell as described previously in Section 2.1.4. Pregnancy status also was assessed as described in Section 2.1.4.

The study was considered a success if both the point estimate and the upper limit of 95% CI are less than the expected pregnancy rate.

Additional Secondary Efficacy Endpoints

1) Pregnancy rate within 120 hours of UPI: The same primary efficacy analysis was performed for the subjects who took Ulipristal within 120 hours of UPI.

2) **Prevented fraction:** The prevented fraction of pregnancies was calculated in the same manner as in Study HRA2914-509.

3) **Trend in pregnancy rates:** Pregnancy rates were calculated for each of the five 24-hour intervals ranging from 0 hours to 120 hour between UPI and study medication intake.

4) **Non-Inferiority to levonorgestrel:** The non-inferiority of Ulipristal versus levonorgestrel as EC was concluded if the upper bound of the 95% confidence interval of the odds ratio of pregnancy in Ulipristal group and levonorgestrel group was lower than the non-inferiority margin of 1.6. The superiority was established if the upper bound of the 95% confidence interval of the odds ratio is below 1.0.

The odds ratio and its 95% confidence interval were estimated based on a logistic regression model, which includes the Trussell's conception probabilities (pooled recognizable set) as adjustment. Each patient's conception probability was determined by her cycle day of intercourse, where the greatest conception probability was taken in case of multiple unprotected intercoursures in the study window.

Missing Data

Missing pregnancy status was treated as not pregnant in the mITT analysis population; other missing data was not imputed.

Sensitivity analysis

In order to assess the impact of lost-to-follow-up on efficacy results, the primary efficacy endpoint was repeated on mITT interim, mITT, mITT2, and ITT Completer populations.

The pregnancy status for lost-to-follow-up subjects was imputed according to the following two approaches:

- Lost-to-follow-up subjects were considered pregnant.
- Lost-to-follow-up subjects were considered as having the same proportion of pregnancy as the expected pregnancy rate estimated based on Trussell's conception probabilities.

Pooled Analyses

The applicant also conducted analyses by pooling data from both studies HRA2914-513 and HRA2914-509. However, we consider results from each study as primary and results of pooled analyses as secondary.

Subgroup analyses

No subgroup analyses were performed by the applicant in this submission.

Interim analysis

An interim analysis was planned when 1200 mITT subjects who took either Ulipristal or levonorgestrel within 72 hours of UPI have completed the study. The interim and final analyses were performed using the Lan DeMets' alpha spending function approach, O'Brien-Flemming spending function and an information fraction of $1200/1654 = 0.72$. The critical value for the interim analysis was set to $z_{0.025} = 2.3876$ which corresponds to a probability level of 0.01696

and for the final analysis $z_{0.025} = 2.0056$ (instead of 1.96) which corresponds to a nominal alpha of 0.02245 and a cumulated exit probability of 0.05 for a one-sided test or to a nominal alpha of 0.0449 for a two-sided test. Therefore, 95% confidence intervals presented for primary efficacy analyses were adjusted for interim and final analyses.

2.3 Data Sources

The study reports and additional information for this submission are available in electronic format. The SAS data sets are complete and well documented. These items are located in the Electronic Document Room at \\Cdsub1\evsprod\NDA022474.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Study HRA2914-509

3.1.1.1 Study Population

A total of 1623 patients were enrolled in 40 U.S. sites. Of these, 1533 were treated including 1507 who were eligible and 26 who were treated but not eligible. Among the treated subjects, 1362 (88.8%) completed all scheduled study visits as per protocol. The main reason for discontinuation was lost to follow-up 102 (6.7%). The details of the disposition are summarized in Table 4.

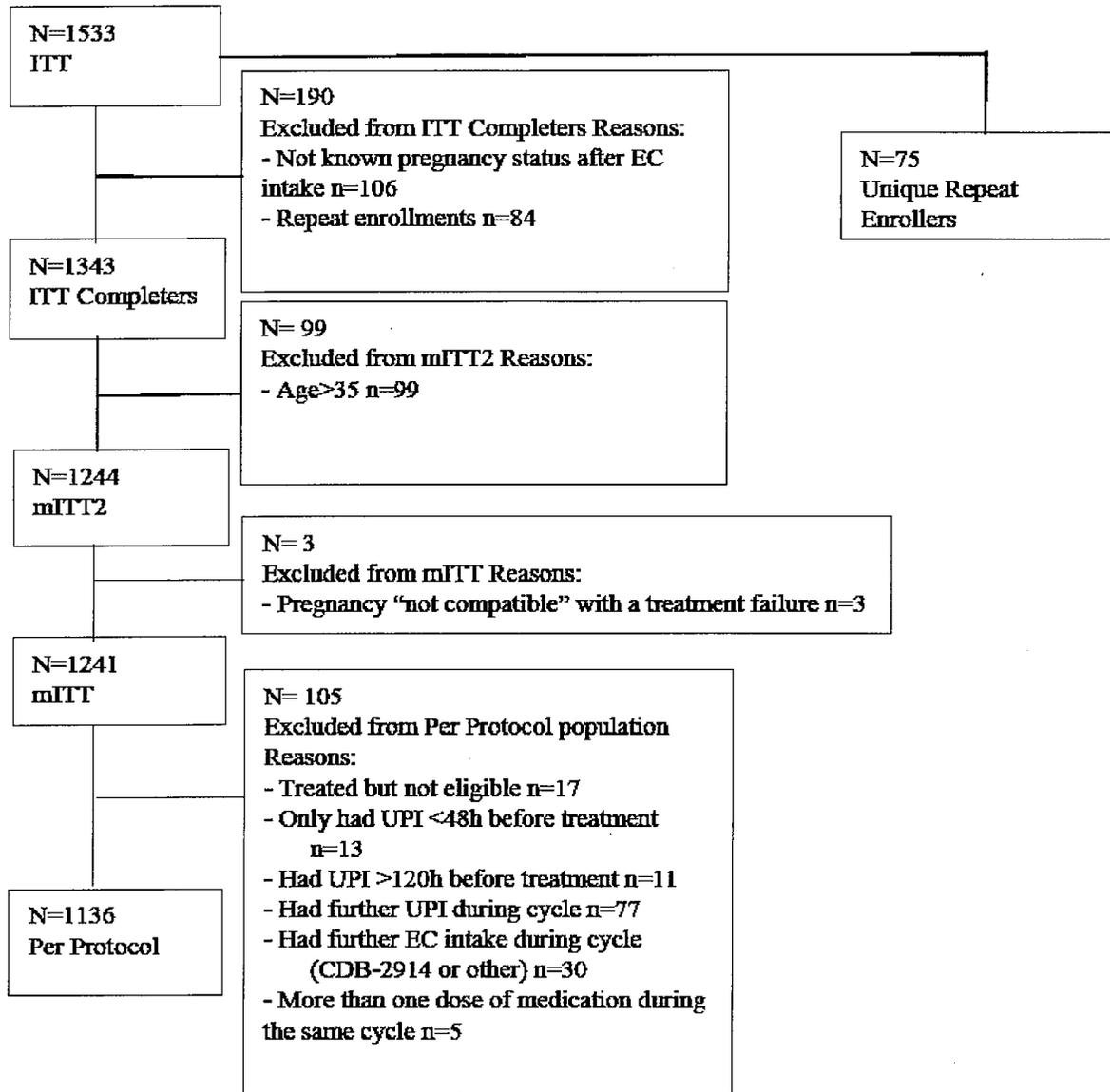
Table 4: Disposition of Subjects: Study HRA291-509

| Category | Ulipristal acetate | |
|--------------------------|--------------------|-------|
| Treated (ITT) | 1533 | |
| Not Eligible but Treated | 26 | |
| Completed the Study | 1362 | 88.8% |
| Discontinued the Study | 171 | 11.2% |
| Reason for Discontinued | | |
| Lost to follow-up | 102 | 6.7% |
| Withdrew consent | 1 | 0.1% |
| Adverse event | 0 | 0.0% |
| Others | 68 | 4.4% |

(Source: Sponsor and Reviewer's Analysis)

Details of the analysis populations are shown in Figure 1. Of the 1533 treated patients, a total of 1244 subjects were eligible for the modified Intent-To-Treat population (mITT2) population, in which there were 3 pregnancies deemed to be “not compatible” and, therefore, excluded from the applicant’s mITT population.

Figure 1: Flow Chart of Analysis Populations: Study HRA291-509



(Source: Clinical Study HRA291-509 Report; Flow Chart2. page 31)

Reviewer's Comment

- The Applicant's mITT2 population (N=1,244) included three additional subjects who were subsequently excluded from the mITT population because their pregnancies were determined by the DSMB to be "not compatible" with EC failure.
- The Division concluded that EC failure could not be completely excluded in one of the three pregnancies deemed "not compatible" with an EC failure by the DSMB. The Division agreed that the other two pregnancies were pre-existing at the time of treatment. Therefore, the FDA efficacy population consisted of 1242 subjects.

3.1.1.2 Demographic and Baseline Characteristics

Demographic and gynecological histories of all the treated subjects were presented in Table 5. The mean age was 24.4 years (range 18 – 50) and most women fell into two age categories: 18-20 years (29.1%) and 21-25 years (39.9%). The majority of patients were Caucasian (60.3%) and black or African American (20%). The mean weight of the patients was 68.3 kg and the mean BMI was 25.3 (range 16.1 – 61.3).

The average menstrual cycle length reported at inclusion was 29.0 days (range 24 - 35 days). The majority of subjects (96.0%) had regular periods in the previous year with an average of 4.7 bleeding days. The primary contraceptive method was male condom (71.7%) and none (17.9%) in the past three months at inclusion; 52.5% of subjects had used EC prior to study entry.

Table 5: Demographics and Baseline Characteristics (ITT): Study HRA2914-509

| Variables | ITT Population (N=1533) |
|---|---|
| Age (Years) | Mean (±SD) 24.4±6.1 Median Age=23 Min-Max=18-50 |
| Age Category | |
| 18-35 | 93.5% |
| 36 and older | 6.5% |
| Race | |
| White | 60.3% |
| African American | 21.5% |
| Asian | 2.3% |
| Other | 13.9% |
| Body Mass index (kg/m²) | Mean (±SD) 25.3±6.2 Median BMI=23.5 Min-Max=16.1-61.3 |
| Average menstrual length (days) | Mean 29.0 (range 24.0-35.0) |
| Average number of bleeding days | Mean 4.7 (range 2.0-10.0) |
| Primary Contraceptive Method | |
| Male Condom | 71.7% |
| None | 9.4% |
| Other | 18.9% |
| Previous EC use | 52.5% |
| Previous pregnancy | 52.4% |
| Previous live birth | 33.6% |

(Source: Adapted from Clinical Study HRA2914-509 Report; Table 2, page 33, 35, 37)

The coital history within 120 hours of treatment is summarized in Table 6. Of the 1533 subjects included in the ITT population, prior to inclusion 1,301 (84.9%) of them had one unprotected intercourse, 172 (11.2%), 36 (2.3%) and 13 (0.8%) of them had 2, 3 and 4 unprotected intercourses, respectively. One subjects (0.1%) had 5 or greater than 5 unprotected intercourses before treatment.

Table 6: Coital History between 48 and 120 hours (ITT): Study HRA291-509

| | | ITT N=1533 |
|---|----------|---------------|
| NUMBER OF UNPROTECTED INTERCOURSES PER SUBJECT | N | 1533 |
| | 0 | 9 (0.6%) |
| | 1 | 1301 (84.9%) |
| | 2 | 172 (11.2%) |
| | 3 | 36 (2.3%) |
| | 4 | 13 (0.8%) |
| | 5 | 1 (0.1%) |
| | 5+ | 1 (0.1%) |
| ALL INTERCOURSES PROTECTED | N | 1533 |
| | YES | 9 (0.6%) |
| | NO | 1524 (99.4%) |

(Source: Clinical Study HRA291-509 Report; Table 1.6.2 page 214)

The subject distribution between 48 and 120 hours of treatment time window (24 hours) for mITT population for Study HRA291-509 is summarized in Table 7. Because this study was specifically designed to evaluate efficacy in the time frame 48-120 hours, the exclusion of the time frame 0 to 48 hours after UPI was lead to more women in the time frame 72 - 120 hours after UPI.

Table 7: Number of Subjects Presenting for EC by 24-hour Time Interval after UPI (mITT and FDA Efficacy Population): Study HRA-2914-509

| Time Interval from UPI to Use of EC (hours) | Applicant's mITT Population | FDA Efficacy Population |
|---|-----------------------------|-------------------------|
| | N=1241 n (%) | N=1242 n (%) |
| 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: Reviewer's Analysis)

3.1.1.3 Primary Efficacy Results

The results of the primary efficacy analysis, the pregnancy rate, based on the Applicant's mITT populations and the FDA efficacy population for subjects treated between 48 and 120 hours of UPI are shown in Table 8.

Based on Applicant's mITT population, the observed pregnancy rate was 2.10% with the upper bound of the 95% CI (1.41%, 3.10%) not exceeding 4%, a clinical relevance threshold generally set to demonstrate efficacy in an uncontrolled study. This observed pregnancy rate was statistically significantly lower than the calculated expected pregnancy rate of 5.53%.

Based on FDA analysis population, the observed pregnancy rate was 2.17% (95% CI: 1.47%, 3.19%). The upper bound of 95% CI 3.19% was not exceeding the calculated expected pregnancy rate of 5.53% and clinical relevance threshold of 4%.

Therefore, the results support the efficacy of Ulipristal in reducing the risk of pregnancy when taken within 48-120 hours after UPI.

Similar results (not shown here) were also seen based on the analysis using mITT2, PP, and ITT Completers analysis populations.

Table 8: Pregnancy Rates (95% CI) 48 - 120 hours after UPI (mITT and FDA Efficacy Population): Study HRA291-509

| | Applicant's mITT Population N=1241 | FDA Efficacy Population N=1242 |
|---|---|---|
| Estimated Expected Pregnancies per Trussell (n) | 69 | 69 |
| Estimated Expected Pregnancy Rate (%) | 5.53 | 5.53 |
| Observed Pregnancies (n) | 26 | 27 |
| Observed Pregnancy Rate (%) (95% CI) | 2.10 (1.41, 3.10) | 2.17 (1.47, 3.19) |

(Source: Clinical Study HRA291-509 Report; Table 8 page 41)

3.1.1.4 Secondary Efficacy Results

Prevented Fraction

The proportion of pregnancies prevented by treatment with Ulipristal 48 to 120 hours after UPI based on both the Applicant's mITT and FDA efficacy populations are presented in Table 9. The prevented fractions of expected pregnancies were 62.3% and 60.9% for Applicant's mITT and FDA Efficacy Population, respectively.

Table 9: Prevented Fraction (95% CI) 48 - 120 hours after UPI (mITT, mITT2): Study HRA291-509

| Population | Subjects Exposed (N) | Observed Pregnancies (n) | Expected Pregnancies (n) | Prevented Fraction (%, 95% CI) |
|--------------------------------|-------------------------------------|---|---|---|
| Applicant's mITT | 1241 | 26 | 69 | 62.3 (41.9, 75.6) |
| FDA Efficacy Population | 1242 | 27 | 69 | 60.9 (40.1, 74.5) |

(Source: Clinical Study HRA291-509 Report; Table 12.1 page 427 & 428)

Trend in pregnancy rates

Estimates of the pregnancy rates over the three 24-hour time intervals between 48 to 120 hours from UPI are summarized in Table 10. The estimates of the pregnancy rates were 2.45%, 2.05% and 1.27% respectively at 48 to 72 hours, 73 to 96 hours, and 97 to 120 hour intervals.

Table 10: The Observed Pregnancy Rates at 24-hour Time Intervals in Subjects Treated with Ulipristal (FDA Efficacy Population): Study HRA291-509

| 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 | 1242 | 27 | 2.17 (1.47, 3.19) | 69 | 5.53 |

(Source: Reviewer’s Analysis)

3.1.2 Study HRA2914-513

3.1.2.1 Study Population

A total of 2321 subjects were screened, and 2221 subjects were treated: 1104 subjects treated with Ulipristal including 10 who were treated but not eligible, 1117 subjects treated with levonorgestrel including 14 who were treated but not eligible. Among the 1104 Ulipristal treated subjects, 1013 (91.8%) completed all scheduled study visits. The main reason for discontinuation was lost to follow-up 36 (4.3% of treated subjects). Among the 1117 levonorgestrel treated subjects, 1046 (93.6%) completed all scheduled study visits. Of the 71 (6.4%) treated subjects who discontinued the study, 40 were lost to follow-up (corresponding to 3.6% of treated subjects). The details of the disposition are summarized in Table 11.

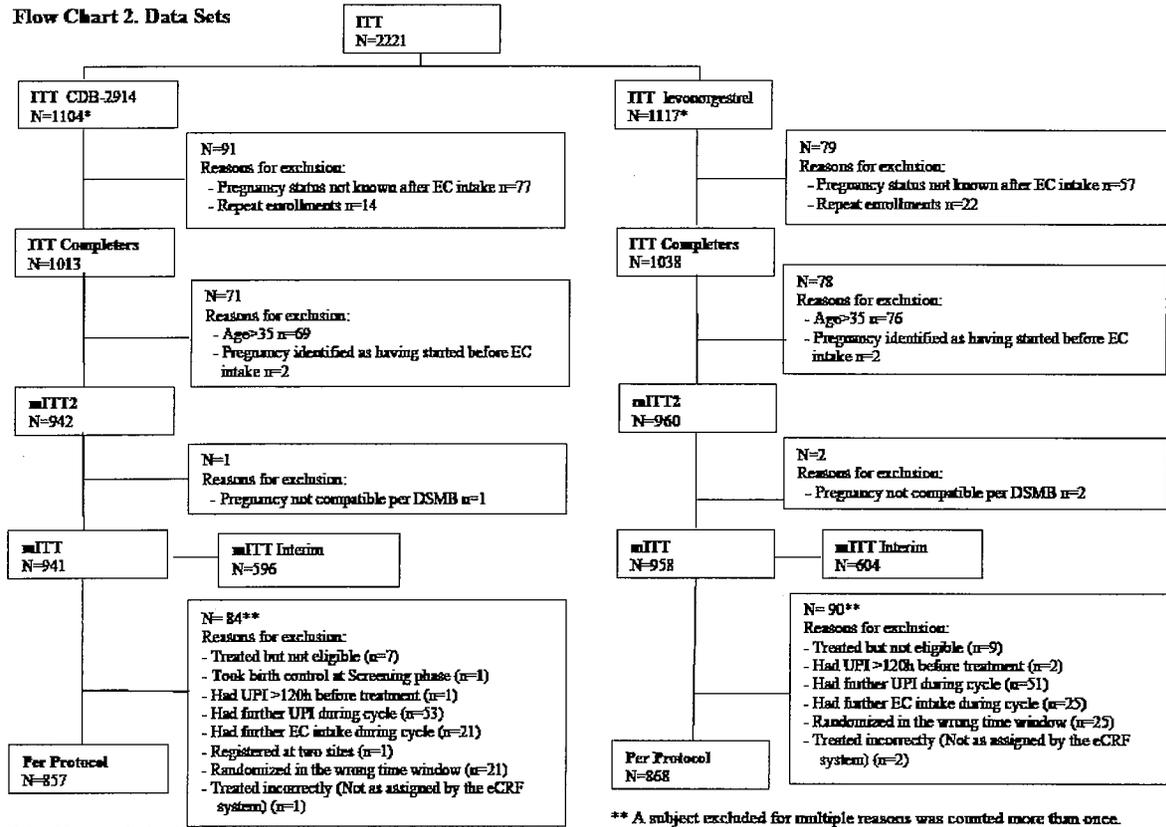
Table 11: Patient Disposition (ITT): Study HRA2914-513

| Category | Ulipristal acetate | | Levonorgestrel | | Total | |
|--------------------------|--------------------|-------|----------------|-------|-------|-------|
| Treated (ITT) | 1104 | | 1117 | | 2221 | |
| Not Eligible but Treated | 10 | | 14 | | 24 | |
| Completed the Study | 1013 | 91.8% | 1046 | 93.6% | 2059 | 92.7% |
| Discontinued the Study | 91 | 8.2% | 71 | 6.4% | 162 | 7.3% |
| Reason for Discontinued | | | | | | |
| Lost to follow-up | 48 | 4.3% | 40 | 3.6% | 88 | 4.0% |
| Withdrew consent | 5 | 0.5% | 1 | 0.1% | 6 | 0.3% |
| Adverse event | 2 | 0.2% | 0 | 0.0% | 2 | 0.1% |
| Others | 36 | 3.3% | 30 | 2.7% | 66 | 3.0% |

(Source: Sponsor and Reviewer’s Analysis)

Disposition of patients in the analysis populations are shown in Figure 2. Of the 2221 treated patients, 2051 were included in ITT completer population with known pregnancy status after EC intake excluding repeat enroller. A total of 69 subjects in the Ulipristal and 76 subjects in the levonorgestrel group aged >35 years were excluded from the mITT2 population. In addition, 3 more subjects were excluded, because their pregnancies were deemed to be “not compatible”.

Figure 2: Flow Chart of Analysis Populations: Study HRA291-513



* A subject enrolled twice but into a different treatment group, was counted as independent for each treatment group, but only once for overall.

(Source: Clinical Study HRA291-513 Report; Flow Chart 2, page 14)

Comments

1. According to the DSMB, one pregnancy in the ulipristal group and two pregnancies in the levonorgestrel group (one pregnancy occurred in a subject treated 0-72 hours after UPI, another pregnancy occurred in a subject treated 73-120 hours after UPI) were not compatible with EC failure.
2. Of these three "not compatible" pregnancies, the Division concluded that EC failure could not be completely excluded for the one pregnancy in the ulipristal group. The Division, however, concurs with the DSMB that the 2 pregnancies in the levonorgestrel group were not compatible with EC failure.
3. Therefore, secondary efficacy analyses of the Final Study data in this Document were based on the Final FDA efficacy population comprised of:
 - ulipristal: 844 subjects (0-72 hours, 16 pregnancies total) and 940 subjects (0-120 hours, 16 pregnancies total)
 - levonorgestrel: 851 subjects (0-72 hours, 22 pregnancies) and 954 subjects (0-120 hours, 25 pregnancies total)

3.1.2.2 Demographic and Baseline Characteristics

Demographic and gynecological histories of all treated subjects were presented in Table 15. The mean age was 24.7 years (range 16 – 55). The majority of patients were Caucasian (72.6%) and black or African American (18.8%). The mean weight of the patients was 68.0 kg and the mean BMI was 25.3 (range 14.9 – 70.0). The average menstrual cycle length reported at inclusion was 28.0 days (range 23 - 40 days). The majority of subjects (Ulipristal, 98.6%; levonorgestrel, 98.7%) had regular periods in the previous year with an average of 4.7 bleeding days. The primary contraceptive method was male condom (Ulipristal, 82.1%; levonorgestrel, 83.7%) and none (12.7%) in the past three months at inclusion; 55.3% of subjects had used EC prior to study entry.

Table 12: Demographics and Baseline Characteristics (ITT): Study HRA2914-513

| Variables | Ulipristal Acetate N=1104 | Levonorgestrel N=1117 |
|--|--|--|
| Age (Years) (SD) | 24.5 ± 6.1 Median Age: 23.0 Min-Max: 16-52 | 24.9 ± 6.5 Median Age: 23.0 Min-Max: 16-55 |
| Age Category (%) | | |
| 16-17 | 4.0 | 4.4 |
| 18-35 | 89.5 | 88.2 |
| 36 and older | 6.5 | 7.4 |
| Race (%) | | |
| White | 72.8 | 72.4 |
| African American | 19.0 | 18.5 |
| Asian | 1.2 | 1.9 |
| Other | 7.0 | 7.2 |
| Body Mass index (kg/m²) (SD) | 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 |
| Average menstrual length (days) | 28.7 (24-35) | 28.8 (23-40) |
| Previous EC use | 54.9% | 55.7% |
| Previous pregnancy | 47.3% | 47.8% |
| Previous live birth | 31.5% | 32.8% |

(Source: Adapted from Clinical Study HRA291-513 Report: Table 4, page 42 & 43)

The coital history within 120 hours of treatment is summarized in Table 13. Of the 2221 ITT subjects, 1975 (Ulipristal, 89.4%; levonorgestrel, 88.5%) subjects had one UPI, 84 (Ulipristal, 7.5%; levonorgestrel, 9.0%), 44 (Ulipristal, 2.1%; levonorgestrel, 1.9%) and 14 (Ulipristal, 0.9%; levonorgestrel, 0.4%) subjects had 2, 3 and 4 UPIs, respectively, no subject had 5 UPIs. Four (Ulipristal, 0.1%; levonorgestrel, 0.3%) subjects did not have any recorded UPI before treatment.

Table 13: Coital History within 120 hours (ITT): Study HRA291-513

| | | DOB-2914 N=1104 | LEVONORGESTREL N=1117 | OVERALL N=2221 |
|---|------------|----------------------------|----------------------------------|---------------------------|
| Number of Unprotected Intercourses per Subject | N | 1104 | 1117 | 2221 |
| | 0 | 1 (0.1%) | 3 (0.3%) | 4 (0.2%) |
| | 1 | 987 (89.4%) | 988 (88.5%) | 1975 (88.9%) |
| | 2 | 83 (7.5%) | 101 (9.0%) | 184 (8.3%) |
| | 3 | 23 (2.1%) | 21 (1.9%) | 44 (2.0%) |
| | 4 | 10 (0.9%) | 4 (0.4%) | 14 (0.6%) |
| | 5 | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| | 5+ | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Contraceptive Used | N | 1103 | 1114 | 2217 |
| | Yes | 484 (43.9%) | 500 (44.9%) | 984 (44.4%) |
| | No | 619 (56.1%) | 614 (55.1%) | 1233 (55.6%) |

(Source: Clinical Study HRA291-513 Report; Table 1.6.2, page 118)

The subject disposition within 120 hours of treatment time window (24 hours) for Final FDA Efficacy population is summarized in Table 14. Because only about 10% of the total enrolled patients were taking EC between 72 and 120 hours, the focus of the review for this study is on UPI time window between 0 and 72 hours.

Table 14: Number of Subjects (%) by 24-hour Time Interval between UPI and EC Treatment (Final FDA Efficacy Population): Study HRA291-513

| Time Interval from UPI to Use of EC (hours) | Ulipristal acetate Subjects N=940 n (%) | Levonorgestrel Subjects N=954 n (%) | Total Subjects N=1894 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: Reviewer's Analysis)

In general, the treatment groups were generally similar with regard to demographic, gynecological history, coital history and other baseline characteristics.

3.1.2.3 Primary Efficacy Results

As stated earlier, a pre-specified interim analysis was performed on the first 1200 mITT subjects enrolled within 72 hours of UPI. Interim analyses results (inferiority to the expected pregnancy rate, inferiority to 4% and non-inferiority to levonorgestrel) were all conclusive, and the study was stopped, because the study was considered a success as per interim analysis plan pre-specified in the protocol. At the time of the interim analysis (Feb 2, 2009), the planned sample size was close to completion. Therefore, data from these latter subjects, in conjunction with the data from the subjects included in the interim analysis were included in the final (or complete) database. But analysis based on the interim database was considered "primary" and analysis based on final database was considered supportive.

Primary Analysis (Interim):

The results of the primary efficacy analysis based on the mITT interim population are presented in Table 15. In the Ulipristal treatment group, the observed pregnancy rate (9 pregnancies) for mITT Interim population (N = 596) was 1.51% (95% CI; 0.62%, 3.32%). This observed pregnancy rate was statistically significantly lower than the calculated expected pregnancy rate of 5.63% and lower than the clinical relevance threshold of 4%. In the levonorgestrel treatment group, there were 17 confirmed pregnancies for mITT Interim population (N = 604) and the observed pregnancy rate was 2.81% (95% CI; 1.54%, 4.97%).

Table 15: Pregnancy Rate (95% CI) after EC Treatment 0 – 72 hours after UPI (mITT Interim): Study HRA291-513

| | 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 |
| Observed pregnancy rate (%) (95% CI) * | 1.51 (0.62 - 3.32) | 2.81 (1.54 - 4.97) |

*95% CI adjusted for interim analysis with the critical value set to $Z_{0,025}=2.3876$.
(Source: Clinical Study HRA291-513 Report; Table 7, page 54 & 55)

Comments

1. *We concur with the Applicant's decision that the efficacy analyses based on the interim database would be the "primary" analyses, since the study was stopped for demonstrating efficacy of ulipristal.*
2. *The DSMB concluded that none of the observed pregnancies in either the ulipristal or levonorgestrel group in the mITT interim population was "not compatible" with an EC treatment failure and all observed pregnancies were included in the mITT interim population. Thus, the Applicant's interim mITT and the FDA interim efficacy populations were identical.*

Final Analysis (Supportive):

The Final database included 16 and 22 pregnancies in the Ulipristal and levonorgestrel group based on FDA Efficacy Population. The observed pregnancy rates were 1.90% (CI: 1.13%, 3.12%) and 2.59% (CI: 1.68%, 3.94%) in the Ulipristal and levonorgestrel 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 (Ulipristal: 5.55%, levonorgestrel: 5.43%). The upper limit of the 2-sided 95% CI of the observed pregnancy rate was lower than the Applicant's clinical relevance threshold of 4% for both treatment groups.

In the Final Study, per applicant, 15 and 22 pregnancies occurred in the Ulipristal (N=843) and levonorgestrel (N=851) groups, respectively, for the mITT population. The observed pregnancy rate for the Ulipristal group was 1.78% (95%: 1.04, 2.98) compared to pregnancy rate of 2.59%

(95% CI: 1.68, 3.94) for the levonorgestrel group. The upper limit of the 2-sided 95% CI of the observed pregnancy rate was lower than the expected pregnancy rate and clinical relevance threshold of 4% for both treatment groups.

Similar results (not shown here) were also seen based on analysis using mITT2, PP, and ITT Completers populations.

Table 16: Pregnancy Rate (95% CI) after EC Treatment within 72 hours of UPI: Study HRA291-513

| | 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) * | 1.78 (1.04, 2.98) | 1.90 (1.13, 3.12) | 2.59 (1.68, 3.94) |

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

(Source: Clinical Study HRA291-513 Report; Table 8, page 57 & 58 and Reviewer's Analysis)

3.1.2.4 Secondary Efficacy Results

This section presents the sponsor's results for pregnancy rate within 120 hours of UPI, prevented fraction and trend in pregnancy rates.

Pregnancy rate within 120 hours of UPI

As shown in Table 17, in the Ulipristal treatment group, the observed pregnancy rate within 120 hours of UPI for mITT population (N = 939) was 1.60% (95% CI; 0.93%, 2.67%). This observed pregnancy rate was statistically significantly lower than the calculated expected pregnancy rate of 5.72% and lower than the clinical relevance threshold of 4%. In the levonorgestrel treatment group, the observed pregnancy rate for mITT population (N = 954) was 2.62% (95% CI; 1.75%, 3.89%).

Table 17: Pregnancy Rate (95% CI) after EC Treatment within 120 hours of UPI: Study HRA291-513

| | 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: Clinical Study HRA291-513 Report; Table 8, page 57 & 58 and Reviewer's Analysis)

Prevented fraction

The prevented fractions of pregnancies within 72 hours and 120 hours of UPI for the mITT population were 68.1% (95% CI; 45.8 - 81.2) and 72.2% (95% CI; 52.8 – 83.7), respectively. The prevented fraction of pregnancies in the Final FDA efficacy population was 66.0% (95% CI: 42.5 to 79.9%) when Ulipristal 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.

Table 18: Prevented Fractions (Contraceptive Effectiveness): Study HRA291-513

| 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 | 68.1 (45.8, 81.2) | 66.0 (42.5, 79.9) | 52.2 (25.1, 69.5) |
| 0-120 hrs | 72.2 (52.8, 83.7) | 70.4 (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: Clinical Study HRA291-513 Report; Table 10, page 63 and Reviewer's Analysis)

Trend in pregnancy rates

The trend in pregnancy rates was evaluated in five 24 hour intervals for Final FDA efficacy population. The observed pregnancy rates for the Ulipristal treatment group were 1.60%, 2.13% and 1.96%, respectively at 0-24, >24-48 and >48 to 72 hour time intervals. No pregnancies in the Ulipristal treatment group were observed between 72 and 96 or between 96 to 120 hours interval due to small sample sizes.

Table 19: Pregnancy Rates by 24-Hour Time Interval between UPI and EC Treatment (Final FDA Efficacy Population): Study HRA291-513

| Time from UPI (hours) | Ulipristal acetate | | | Levonorgestrel | | |
|-----------------------|----------------------|--------------------------|------------------------------------|----------------------|--------------------------|------------------------------------|
| | Exposed Subjects (n) | Observed Pregnancies (n) | Pregnancy Rate (%) (95% CI) | Exposed Subjects (n) | Observed Pregnancies (n) | 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: Reviewer's Analysis)

Non-Inferiority of Ulipristal to Levonorgestrel

Based on the mITT interim analysis population, Ulipristal was non-inferior to levonorgestrel when used as EC within 72 hours of UPI as shown by the upper bound of the 95% CI of the odds ratio of the point estimate, which was lower than the non-inferiority margin of 1.6. Superiority was not established because the upper bound of the 95% CI for the odds ratio was not below 1.0.

Table 20: Odds Ratio (95% CI) of Pregnancy Rate in Ulipristal Relative to Levonorgestrel Administered within 72 Hours of UPI (mITT Interim): Study HRA291-513

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

*95% CI adjusted for interim analysis with the critical value set to $Z_{0.025}=2.3876$.
(Source: Clinical Study HRA291-513 Report; Table 9.1.1, page 443)

3.1.3 Reviewer's Comment

This review noted one minor issue in this submission regarding how pregnancies were counted in the efficacy evaluation. In Applicant's mITT population, few pregnancies were excluded because DSMB determined that those pregnancies were "not compatible" with EC failure. But, the Division has also reviewed all such cases and determined that one pregnancy should be included in the efficacy evaluation. Therefore, FDA analysis population included one additional pregnancy in each study.

The efficacy results using Applicant's mITT, mITT2, PP and FDA Efficacy Population showed that observed pregnancy rates were statistically significantly lower than the calculated expected pregnancy rates and met the clinical relevance threshold of < 4% in both studies. Both studies had reasonable dropout rates and recruited an adequate number of subjects for the planned effect size to assess the efficacy of the doses under investigation with at least 80% power.

This review also performed the trend analysis for the five 24-hour intervals from 0-120 hours between UPI and EC in subjected treated with Ulipristal using pooled data from the two phase 3 studies. Although the study was not powered to demonstrate efficacy per 24 hour time frame, these subgroup analyses could be considered supportive of efficacy across the whole time frame of 0 to 120 hours after UPI. The results of the analysis based on the FDA efficacy populations for both studies 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 at 24-hour Time Interval between UPI and EC for Subjects treated with 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 | 5.61 | 63.9 (48.3, 74.7) |

(Source: Reviewer's Analysis)

3.2 Evaluation of Safety

Refer to the clinical reviewer's report for evaluation of safety data.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

To assess the impact of race, age, body mass index group (≤ 30 and $30+$), contraception probability, and cycle day of intercourse, logistic regression model was used by this reviewer. As presented in Table 22, the model indicated a statistically significant impact effect of 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 details.

Table 22: Results of Logistic Regression Model (FDA Efficacy Population): Study HRA291-513

| 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: Reviewer's Analysis)

Based on the above result, we conducted subgroup analyses by race, age, region, and BMI group. In summary, the treatment effects were inconsistent among the subgroup of BMI.

4.1 Race

Due to small number of subjects in minority and other ethnic category, no definitive conclusion could be drawn.

Table 23: Pregnancy Rate (95% CI) in Subjects treated with Ulipristal within 120 hours of UPI by Race (Pooled Phase 3 Studies)

| Race | 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 (%) |
| White | 20 / 1450 | 2.07 (1.43, 2.97) | 5.77 | 19 / 689 | 2.76 (1.73, 4.34) | 5.25 |
| Black | 10 / 432 | 2.31 (1.18, 4.33) | 5.05 | 5 / 174 | 2.87 (1.01, 6.86) | 6.41 |
| Others | 3 / 300 | 1.00 (0.18, 3.11) | 5.66 | 1 / 91 | 1.10 (-0.44, 6.77) | 5.83 |

(Source: Reviewer's Analysis)

4.2 Age

Subgroup analyses by age group (< 18, 18 to 35, and > 35 years old) for Study HRA2914-513 individually and pooled with Study HRA2914-509 are presented in Table 24 and Table 25, 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 24: Pregnancy Rate (95%) within 72 hours of UPI by Age Group (Final FDA Efficacy Population): Study HRA2914-513

| 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: Reviewer's Analysis)

Table 25: Pregnancy Rate (95%) in Subjects treated with Ulipristal within 120 hours of UPI by Age Group (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) | 133 | 5.67 | 66.2 (51.9, 76.2) |

(Source: Reviewer's Analysis)

4.3 Region

This reviewer also performed subgroup analysis by region for Study HRA2914-513 only (see Table 26). Study HRA2914-509 was conducted in the US. In both US and European region, the upper limits of the 95% CIs in subjects treated with Ulipristal were consistently lower than the respective expected pregnancy rate and lower than the clinical relevance threshold of 4%. The pregnancy rate in subjects treated with Ulipristal was lower in Europe compared to US.

Table 26: Pregnancy Rate (95%) in Subjects treated with Ulipristal within 120 hours of UPI by Region (Final FDA Efficacy Population): Study HRA2914-513

| Region | Ulipristal acetate | | | Levonorgestrel | | |
|--------|------------------------|--------------------------------------|-----------------------------|------------------------|--------------------------------------|-----------------------------|
| | Pregnancies / Subjects | Observed Pregnancy Rate (%) (95% CI) | Expected Pregnancy Rate (%) | Pregnancies / Subjects | Observed Pregnancy Rate (%) (95% CI) | Expected Pregnancy Rate (%) |
| US | 12 / 553 | 2.17 (1.18, 3.85) | 5.21 | 13 / 545 | 2.39 (1.34, 4.13) | 5.12 |
| Europe | 4 / 291 | 1.37 (0.39, 3.69) | 6.19 | 9 / 306 | 2.94 (1.44, 5.66) | 6.00 |

(Source: Reviewer's Analysis)

4.4 BMI Subgroup

Observed and estimated expected pregnancy rates by BMI ($\leq 30 \text{ kg/m}^2$ or $> 30 \text{ kg/m}^2$) are presented for each of the two phase 3 studies as well as for the pooled phase 3 data (see Table 27). In women with BMI $> 30 \text{ kg/m}^2$, 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 or a lack of efficacy for both Ulipristal and levonorgestrel in the heavier subgroup.

For women with a BMI > 30 kg/m² who received Ulipristal in Study HRA2914-509, 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/m² who received Ulipristal in Study HRA2914-513, 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 levonorgestrel within 72 hours after UPI appeared to be greater than that in Ulipristal treated subjects. For women with a BMI > 30 kg/m² who received levonorgestrel within 72 hours after UPI in Study HRA2914 513, the upper bound of the 95% CI for the observed pregnancy rate (13.42%) also was greater than the estimated expected pregnancy rate of 4.38%.

Table 27: Summary of Pregnancy Rate (95% CI) Between UPI and EC by Study and BMI Group (≤ 30 kg/m² or > 30 kg/m²) (FDA Efficacy Populations)

| 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 (%) |
| HRA2914-509* | BMI ≤ 30 | 21 / 1035 | 2.03 (1.30, 3.13) | 5.76 | NA | | |
| | BMI > 30 | 6 / 207 | 2.90 (1.15, 6.45) | 4.37 | | | |
| | 48 – 120 Hour Total | 27 / 1242 | 2.17 (1.47, 3.19) | 5.25 | | | |
| HRA2914-513** | BMI ≤ 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, 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 / 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, 5.68) | 4.48 | 11 / 154 | 7.14 (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: Reviewer's Analysis)

5. SUMMARY AND CONCLUSIONS

Two phase 3 studies (HRA2914-509 and HRA2914-513) were submitted to support the efficacy of Ulipristal acetate 30 mg as an emergency contraception up to 120 hours following unprotected intercourse or a known or suspected contraceptive failure. Results from the Applicant and FDA analysis confirmed that study HRA2914-509 provided the evidence that Ulipristal was effective for EC when taken 48 to 120 hours after UPI, while study HRA2914-513 provided the evidence that Ulipristal was also effective for EC when taken 0 to 72 hours after UPI.

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 BMI > 30 kg/m².

| 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/

KATE L DWYER
07/22/2010

MAHBOOB SOBHAN
07/22/2010

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 22-474 **Applicant:** Laboratoire HRA Pharma **Stamp Date:** Oct. 14, 2009

Drug Name: Ulipristal Acetate **NDA/BLA Type:** NDA

Indication: Emergency contraception within 120 hours (b) (4) of unprotected intercourse or contraceptive failure

On **initial** overview of the NDA/BLA application for RTF:

| | Content Parameter for RTF | Yes | No | NA | Comments |
|----|--|-----|----|----|--------------------------------|
| 1A | Paper Submission: Index is sufficient to locate necessary reports, tables, data, etc. | X | | | |
| 1B | Electronic Submission: Indexing and reference links within the electronic submission are sufficient to permit navigation through the submission, including access to reports, tables, data, etc. | X | | | |
| 2 | ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.) | X | | | |
| 3 | Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated. | | | X | All female of reproductive age |
| 4 | Data sets in EDR are accessible and conform to applicable guidances (e.g., existence of define.pdf file for data sets). | | X | | See information requests below |

THE STATISTICAL SECTION OF THE APPLICATION IS FILEABLE ___Yes___

The NDA is fileable from a statistical perspective.

| Content Parameter (possible review concerns for 74-day letter) | Yes | No | NA | Comment |
|---|-----|----|----|---------|
| Designs utilized are appropriate for the indications requested. | X | | | |
| Endpoints and methods of analysis are specified in the protocols/statistical analysis plans. | X | | | |
| Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available. | | | X | |
| Appropriate references for novel statistical methodology (if present) are included. | | | X | |
| Safety data organized to permit analyses across clinical trials in the NDA/BLA. | X | | | |
| Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate. | X | | | |

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

INFORMATION REQUESTS

1. The submission currently provides only the data listings (raw data) for each study. Also provide the derived datasets used for analyses (analysis datasets) for all studies, particularly those for studies 2914-509 and 2914-513.
2. For studies 2914-509 and 2914-513, the dataset used for the primary efficacy analysis should include the following variables:
 - Subject I.D.
 - Analysis population code (ITT, protocol specified primary efficacy population, PP, etc.)
 - Dates and times of first and last coital encounters (within 120 hours) prior to taking treatment
 - Date test product was taken
 - Number of hours since first and last coital encounters (within 120 hours) that treatment was taken
 - Pregnancy status (Y/N/uncertain) after taking treatment
 - Age
 - Race
 - Weight
 - BMI
 - Flag if subject was re-enrolled in the study
 - Number of times the subject re-enrolled
 - Variable identifying the re-enrollment occurrence (first time, second time, etc.)
3. Provide the location of the programs used to implement the primary endpoint and important secondary endpoint analyses. If they are not in the application, then submit them.
4. Provide the location of the output from the primary endpoint and important secondary endpoint analyses. If they are not in the application, then submit them.
5. Clarify why there are no dates on the signature pages for all protocols, statistical analysis plans, and amendments.

| | |
|---------------------------------|---------------|
| Sonia Castillo | Nov. 24, 2009 |
| _____ Reviewing Statistician | _____ Date |
| Mahboob Sobhan | Nov. 24, 2009 |
| _____ Supervisor/Team Leader | _____ Date |

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/

SONIA CASTILLO
12/15/2009