OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 022474	Submission Dates: 10/15/2009, 1/19/2010, 4/05/2010, 05/11/2010, 06/29/2010
Brand Name	Ella
Generic Name	Ulipristal Acetate
Reviewer	Hyunjin Kim, Pharm.D., M.S.
Team Leader	Myong-Jin Kim, Pharm.D.
OCP Division	Division of Clinical Pharmacology 3
OND Division	Division of Reproductive and Urologic Products (DRUP)
Sponsor	HRA Pharma
Relevant IND	049381
Submission Type, Code	Original, 1S
Formulation; Strength	Tablet; 30 mg
Indication	Emergency contraceptive for prevention of pregnancy following unprotected intercourse or a known or suspected contraceptive failure

A Required Office-Level Clinical Pharmacology Briefing was held on June 14, 2010 in conference room 1211 of White Oak Bldg 51. Attendees included Drs'. Lisa Soule, Pamela K Lucarelli, Lesko J Lawrence, Nancy Hu, Bryant Tran, Gilbert Burckart, Sally Choe, Darrell Abernethy, Ritesh Jain, Manoj Khurana, Christian Grimstein, Dionna Green, Immo Zdrojewski, Sandhya Apparaju, LaiMing Lee, Lei K, Zhang, Julia Cho, Chongwoo Yu, Nam Atiqur Rahman, Lokesh Jain, Kellie S Reynolds, Chinmay Shukla, Edward D Bashaw, Hae Young Ahn, Ronald Orleans, Mehul U Mehta, Myong-Jin Kim and Hyunjin Kim

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1 Executive Summary

The sponsor submitted an original NDA under 505(b)(1) for ulipristal acetate, a new molecular entity (NME) acting on a progesterone receptor. Ulipristal acetate is an orally administered drug, with a proposed indication for the prevention of pregnancy following unprotected intercourse or a known or suspected contraceptive failure. A single 30 mg tablet of ulipristal acetate should be taken as soon as possible, but no later than 120 hours after unprotected intercourse.

In support of this NDA, the sponsor submitted the two phase 3 studies evaluating the safety and efficacy of ulipristal acetate for the proposed indication. In addition, the sponsor submitted 16 Clinical Pharmacology related studies as following: 8 *in vitro* studies elucidating the distribution, metabolism, and drug interaction potential; 8 phase 1 pharmacokinetic (PK) and pharmacodynamic (PD) studies characterizing the PK and mechanism of action of ulipristal acetate; and 2 phase 2 studies.

Ulipristal acetate is highly (> 94 %) bound to plasma proteins. It is metabolized to mono- and di-demethylated metabolites mainly by CYP3A4. In vitro studies suggest that inhibition or induction potential of ulipristal acetate on CYP enzymes is minimal. The proposed mechanism of action is that ulipristal acetate inhibits or delays ovulation, depending on the time of administration in the follicular phase and alters the endometrium in the luteal phase. These PD properties of ulipristal acetate are mediated by its binding to the progesterone receptor.

The results from a food effect study and two phase 3 studies showed that ulipristal acetate can be administered regardless of meal. There are two proposed manufacturing sites (b) (4) and Leon Farma) for ulipristal acetate and the sponsor has conducted a single-dose bioequivalence (BE) study. Sponsor developed three different formulations, micronized tablet, micronized capsule, and unmicronized capsule. The to-be-marketed formulation is micronized tablet.

1.1 Recommendation

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.

1.2 Post Marketing Requirements

An in vivo drug-drug interaction trial of ulipristal acetate with CYP3A4 inducer needs to be conducted.

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

- Single Dose PK of Ulipristal Acetate
  - Following a single dose administration of ulipristal acetate 30 mg micronized tablet in healthy women under fasting conditions, the maximum plasma concentrations (C_{max}) of ulipristal and its active metabolite, 3877A, were reached within 1 hour of administration (range, 0.5 – 2 hours). The mean (±SD) C_{max} values of ulipristal and metabolite 3877A were 176.0 ± 51 and 68.6 ± 38 ng/mL, respectively, The mean (±SD) area under the curve (AUC) values were 556.0 ± 47 and 246.0 ± 24, respectively. The C_{max} and AUC of ulipristal acetate were more than twice the values of those of the 3877A (HRA2914-504).
- Formulation Comparison - Micronized Tablet vs. Unmicronized Capsule
  - Earlier studies including the PD studies were conducted using the unmicronized capsules. The C_{max} and AUC of ulipristal acetate and 3877A following a single dose administration of 10 mg micronized tablet were higher compared to those from a 10 mg unmicronized capsule (HRA2914-501).
    - Ulipristal acetate
      - C_{max}: 56.7 vs. 29.1 ng/mL (95% higher in micronized tablet)
      - $AUC_{0-\infty}$: 189.9 vs. 138.1 ng·h/mL (38% higher in micronized tablet)
    - 3877A
      - C_{max}: 20.5 vs. 10.7 ng/mL (92% higher in micronized tablet)
      - $AUC_{0-\infty}$: 77.5 vs. 62.8 ng·h/mL (23% higher in micronized tablet)
- Effect of Food
  - Administration of ulipristal acetate under a fed conditions reduced the absorption rate of ulipristal, as indicated by 40-45% lower C_{max} and delayed t_{max} of about 2 hours for both ulipristal acetate and 3877A (HRA2914-512). However, food intake increased the extent of absorption as indicated by 20-25% higher AUC of ulipristal and 3877A compared to fasting conditions (HRA2914-512). Phase 3 studies (HRA2914-509 and HRA2914-513) were conducted without restriction for food. Therefore, ulipristal acetate can be administered regardless of meal.
- Metabolism, Distribution, and Elimination
  - Ulipristal acetate is highly bound (> 94 %) to plasma proteins, including high density lipoprotein, α-acid glycoprotein, and non-esterified fatty acid (HRA2914-427, HRA2914-428, and HRA2914-475).
  - Ulipristal acetate is metabolized to mono- and di- demethylated ulipristal acetate. The data indicated that this metabolism is predominantly mediated by CYP3A4. The mono-demethylated ulipristal acetate, 3877A, appeared to exert similar anti-progesterone activity to ulipristal acetate (HRA2914-429, HRA2914-430, and HRA2914-449).
- Drug Interaction Potential

    - The *in vitro* studies show that ulipristal does not inhibit or induce CYP enzymes. Therefore, the sponsor did not conduct any *in vivo* studies to evaluate CYP inhibition or induction potential of ulipristal acetate (HRA2914-430, HRA2914-476, and HRA2914-477).
    - *In vitro* data indicate that the metabolism of ulipristal acetate is predominantly mediated by CYP3A4. Concomitant administration of CYP3A4 inhibitors may inhibit the metabolism of ulipristal acetate and cause increased plasma concentration of ulipristal acetate. In addition, concomitant administration of CYP3A4 inducers may reduce plasma concentrations of ulipristal acetate and may result in decrease in efficacy.
- PD Effects of Ulipristal Acetate: Effects of single dose administration of ulipristal acetate were assessed during the different phases of women's menstrual cycle.
    - Mid-follicular phase (10, 50, and 100 mg unmicronized capsule): Ulipristal acetate suppressed the growth of lead follicle and increased the time from dose to follicular collapse, therefore, delayed ovulation. In addition, it decreased the plasma concentration of estradiol.
    - Late follicular phase (30 mg micronized tablet): Ulipristal acetate reduced the occurrence of follicular rupture and decreased the luteinizing hormone (LH) surge occurrence. Administration of ulipristal acetate prior to ovulation suppressed the plasma concentration of progesterone, but not the plasma concentration of estradiol.
    - Early luteal phase (10, 50, and 100 mg unmicronized capsule): Ulipristal acetate reduced the endometrial thickness without affecting the menstrual cycle lengths.
    - Mid-luteal phase (1, 10, 50, 100, and 200 mg unmicronized capsule): No significant effect on lengths of luteal phase was observed. However, high dose (200 mg unmicronized capsule) ulipristal acetate caused early endometrial bleeding with shorter length of luteal phase which may have been resulted from its anti-progesterone activity.
- Use in Specific Populations
    - The sponsor requested a waiver of pediatric studies for age groups of males and females from birth to 15 years and 11 months.
    - No hepatic or renal impairment studies were conducted.
- Manufacturing sites
    - The to-be-marketed formulation of ulipristal acetate 30 mg micronized tablet will be manufactured at the two different sites; Leon Pharma (Spain) and (b) (4) A single dose BE study (HRA2914-516) showed that the products manufactured at these two sites are bioequivalent.

2 Question Based Review

2.1 General Attributes

Regulatory background

IND 049381 was opened by National Institute of Child Health and Human Development (NICHD) on December 1, 1995. There was a change of the sponsor on March 6, 2006 when HRA Pharma licensed ulipristal acetate from NICHD.

Following studies were submitted.

- *In vitro*
  - Distribution
    - HRA2914-427: *In vitro* binding of [^{14}C]-ulipristal acetate to human plasma proteins and human blood distribution
    - HRA2914-428: *In vitro* binding of [^{14}C]-ulipristal acetate to mouse, rat, rabbit, dog, monkey and human plasma
    - HRA2914-475: 3877A - Extent of binding to rat, monkey and human plasma proteins and partitioning between the plasma and cell fraction of human blood
  - Metabolism
    - HRA2914-429: Metabolism of [^{14}C]-ulipristal acetate in microsomes isolated from female mouse, rat, rabbit, dog, monkey and human
    - HRA2914-430: Identification of the cytochrome P450 enzymes responsible for the *in vitro* metabolism of [^{14}C]-ulipristal acetate and the effect of ulipristal acetate on the activity of specific human cytochrome P450 enzymes
    - HRA2914-449: *In vitro* antiprogestational/antiglucocorticoid activity and progestin and glucocorticoid receptor binding of the putative metabolites and synthetic derivatives of ulipristal acetate and mifepristone
  - Drug Interaction
    - HRA2914-476: Inhibition of 3877A on CYP enzyme activities in pooled human liver microsomes
    - HRA2914-477: Induction effects of ulipristal acetate and 3877A on CYP1A2 and 3A4 activities in fresh human hepatocytes
- Phase 1
  - PK
    - HRA2914-501: Pharmacokinetic comparison of three preparations of the selective progesterone receptor modulator, ulipristal acetate
    - HRA2914-504: Study of the pharmacokinetic profile of a single 30 mg oral dose of ulipristal acetate in healthy volunteers
    - HRA2914-512: An open, randomized, crossover design study comparing the bioavailability of a single 30 mg oral dose of ulipristal acetate given in fed and fasting conditions in healthy volunteers
    - HRA2914-516: A single-dose, open-label, randomized, 2-way crossover bioequivalence study of ulipristal acetate 30 mg tablets manufactured at Leon Farma (Spain) and (b) (4) under fasting conditions in healthy female volunteers
  - PD
    - HRA2914-503: Luteal phase dose-response relationships of the antiprogestin ulipristal acetate in normally cycling women

- HRA2914-505: A single mid-follicular dose of ulipristal acetate, a new antiprogestin, inhibits folliculogenesis and endometrial differentiation in normally cycling women
- HRA2914-506: Endometrial effects of a single early-luteal dose of the selective progesterone receptor modulator, ulipristal acetate
- HRA2914-511: A prospective, randomized, double-blind, cross-over study to compare the capacity to prevent follicular rupture of ulipristal acetate with placebo, when administered after the ovulatory process has been triggered by the LH Surge
- HRA2914-510: A prospective randomized multi-center phase II study of the dose-response effects of continuous administration of low-dose ulipristal acetate parameters of the hypothalamic-pituitary-gonadal axis and the endometrium.

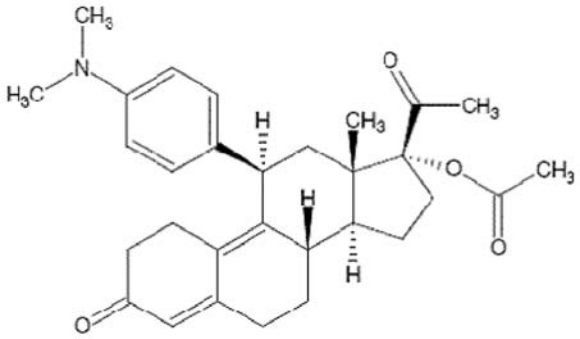
In study HRA2914-510, the study subjects were given 10 mg ulipristal acetate micronized tablets once daily for 3 months. Because the dosing regimen in study HRA2914-510 was different from the dosing regimen in phase 3 clinical studies (HRA2914-509 and HRA2914-513), study HRA2914-509 was not reviewed.

- Phase 2
  - HRA2914-507: A Prospective, randomized, double blind, multi-center study to compare the efficacy, safety and tolerance of ulipristal acetate with levonorgestrel as emergency contraception
  - HRA2914-508: A prospective, randomized, double blind, multi-center study to compare the efficacy, safety and tolerance of 10 mg micronized ulipristal acetate to 50 mg ulipristal acetate as Emergency Contraception
- Phase 3
  - HRA2914-509: A prospective, open-label, single arm, multi-center study to evaluate the efficacy, safety and tolerability of ulipristal acetate 30 mg as emergency contraception when taken between 48 hours and 120 hours of unprotected intercourse
  - HRA2914-513: A prospective, randomized, single blind, multi-center study to compare the efficacy, safety and tolerability of ulipristal acetate with levonorgestrel as emergency contraception within 120 hours of unprotected intercourse

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug product?

<Physico-chemical properties of ulipristal acetate>

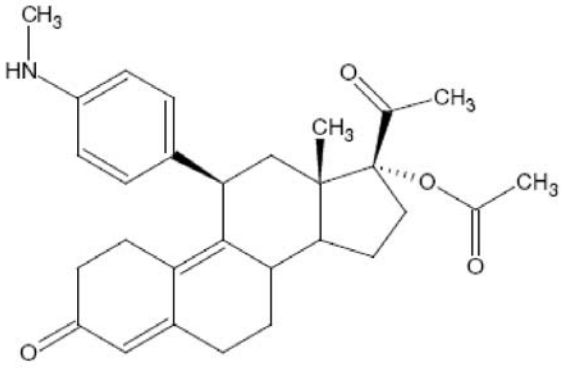
- Structural formula:



- Molecular weight: 475.619
- Molecular formula: $C_{30}H_{37}NO_4$
- Chemical name: 17α-acetoxy-11β-(4-N,N-dimethylaminophenyl)-19-norpregna-4,9-diene-3,20-dione

<Physico-chemical properties of 3877A, an active metabolite of ulipristal acetate>

- Structural formula:



- Molecular weight: 461.619
- Molecular formula: $C_{29}H_{35}NO_4$
- Chemical name: 17α-acetoxy-11β-(4-N-methylaminophenyl)-19-norpregna-4,9-diene-3,20-dione

<Drug Formulation>
The drug product (30 mg micronized tablet) is a white to off-white, round, 9 mm diameter tablet. Each tablet is packaged individually in a colorless transparent aluminum foil blister in a carton box.

Table 1. Composition of ulipristal acetate tablet

Component	Reference to quality standard	Function	Amount per tablet (mg)
Ulipristal acetate	Internal monograph	Drug substance	30.00
Lactose monohydrate	Current NF monograph		(b) (4)
Povidone K30	Current USP monograph		

Croscarmellose sodium	Current NF monograph	[redacted]	
Magnesium stearate	Current NF monograph		
Tablet weight	-	-	300.00

[redacted] uring the process.

There were three formulations (unmicronized capsule, micronized capsule, and micronized tablet) developed during the clinical phase of ulipristal acetate.

The clinical development of ulipristal acetate was initiated by NICHD. NICHD developed its own drug formulation which consisted of unmicronized capsules of various doses (10 – 200 mg). The initial phase 1 PD studies (HRA2914-503, HRA2914-505, and HRA2914-506) as well as the phase 2 studies (HRA2914-507 and HRA2914-508) were conducted with unmicronized capsule. When HRA Pharma became involved in the development of ulipristal acetate in 2001, micronization (micronized capsule and micronized tablet) was introduced as the last step of the manufacturing process to increase the bioavailability of ulipristal acetate. The phase 3 studies (HRA2914-509 and HRA2914-513) were conducted with 30 mg micronized tablet, manufactured at [redacted]

The sponsor did not conduct a bridging study to bridge unmicronized capsule to 30 mg micronized tablet. Therefore, the two phase 2 studies (HRA2914-507 and HRA2914-508) were for descriptive purpose only and were not relied upon for approval of NDA 022474. However, the findings from the three phase 1 PD studies (HRA2914-503, HRA2914-505, and HRA2914-506) were relied upon for approval of NDA022474, since PD properties of 30 mg micronized tablet would be similar to those of unmicronized capsule without being influenced by the formulation difference. *See clinical review by Dr. Orleans Ronald for the review of phase 2 studies (HRA2914-507 and HRA2914-508).*

2.1.2 What is the proposed mechanism of action?

Ulipristal acetate inhibits or delays ovulation, depending on the time of ulipristal administration in the follicular phase, and alters the endometrium in the luteal phase. In addition, high dose ulipristal acetate (200 mg unmicronized capsule) appears to exert an anti-progesterone effect on the ovary and endometrium when it is given in the mid-luteal phase.

The effect of single doses of ulipristal acetate on ovulation and endometrial maturation was evaluated in four phase 1 studies in healthy women with regular menstrual cycles. Three of these four studies (HRA2914-503, HRA2914-505, and HRA2914-506) were sponsored by the NICHD and submitted to the agency in the form of literature. These three studies investigated single doses ranging from 0 to 200 mg of unmicronized ulipristal acetate capsules administered in different phases of the menstrual cycle (mid-follicular, early luteal, or mid-luteal). Study HRA2914-511, sponsored by HRA Pharma (the current NDA holder), evaluated the effect of single dose of the to-be-marketed

formulation of ulipristal (30 mg micronized tablet) administered in the late follicular phase. Pertinent findings follow:

- Mid-follicular phase (HRA2914-505; placebo, 10, 50, and 100 mg unmicronized capsule): Mid-follicular phase was defined as time when the diameter of lead follicle is between 14 – 16 mm.; The size of follicles (by ultrasound) and estradiol concentrations were measured daily from menstrual cycle days 6-8 to follicular collapse in this parallel design study (n=44).
    - When ulipristal acetate (unmicronized capsule) was given in mid-follicular phase (Table 2),
        - growth of lead follicle was suppressed;
        - the time from dose to follicular collapse increased, therefore, ovulation was delayed;
        - the plasma concentration of estradiol decreased.

Table 2. Effect of ulipristal acetate (unmicronized capsule) when it was given in mid-follicular phase; HRA2914-505

	Approximate mean lead follicle diameter on the 4 days after dosing (SD not reported), mm	Days (mean ± SD) from dose to follicle collapse, days	Approximate mean estradiol concentration on the 4 days after dosing (SD not reported), pg/mL
Placebo (n=12)	21.5	5.8 ± 0.6	1,030
10 mg unmicronized capsule (n=11)	21	6.8 ± 1.0	699
50 mg unmicronized capsule (n=11)	17.5	10.3 ± 1.2	405
100 mg unmicronized capsule (n=10)	16.5	12.7 ± 1.0	276

*Approximate mean estradiol concentration in each group (placebo, 10, 50, and 100 mg unmicronized capsule) prior to dosing measured on the day of dosing was between 405 and 423 pg/mL.

- Late follicular phase (HRA2914-511; placebo and 30 mg micronized tablet): Late follicular phase was divided into periods of ovulation (when follicular rupture is imminent with lead follicle size ≥ 18 mm) and LH surge onset (when LH > 8 IU/L for the first time OR LH increased by at least 40% compared to the day before and > 6 IU/L).; The size of follicles (by ultrasound) and hormone concentrations were measured daily from menstrual cycle days 5-8 to 6 days after dosing in this cross over study (n=35).
    - When ulipristal acetate (30 mg micronized tablet) was given in late follicular phase (Table 3),
        - the occurrence of follicular rupture reduced;
        - the occurrence of LH surge reduced;
        - the plasma concentration of estradiol increased;
        - the plasma concentration of progesterone decreased.

Table 3. Effect of ulipristal acetate (30 mg micronized tablet) when it was given in late follicular phase; HRA2914-511

	Administration of ulipristal acetate prior to ovulation				Administration of ulipristal acetate (30 mg micronized) on the day of or after LH surge onset
	Frequency of follicle rupture during the 6 days after dosing, % (n/n)	Frequency of LH surge onset during the 6 days after dosing, % (n/n)	Estradiol concentration during the 6 days after dosing, pmol/L (mean ± SD)	Progesterone concentration during the 6 days after dosing, nmol/L (mean ± SD)	Frequency of follicle rupture during the 6 days after dosing, % (n/n)
Placebo	100 (34/34)	97.1 (33/34)	370.4 ± 207.5	17.9 ± 19.0	100 (19/19)
30 mg micronized tablet	55.8 (19/34)	76.5 (26/34)	420.4 ± 246.6	13.9 ± 18.8	63.2 (12/19)

*Approximate mean concentrations of estradiol and progesterone in each group (placebo and 30 mg micronized tablet) prior to dosing measured on the day of dosing were 530 pg/mL and 4 nmol/L, respectively.

In study HRA2914-505, administration of ulipristal acetate during the mid-follicular phase suppressed the size of lead follicular cell and decreased the plasma concentration of estradiol. These two findings from study HRA2914-505 support each other, since estradiol is mostly secreted by follicular cells. However, study HRA2914-511 showed that estradiol concentration was higher in ulipristal acetate arm when ulipristal acetate was administered in late follicular phase. This may have resulted from the delay of follicular rupture, which in turn increased the time for the follicular cell to produce estradiol

- Early luteal phase (HRA2914-506; placebo, 10, 50, and 100 mg unmicronized capsule): Early luteal phase was defined as one or two days after ovulation (The occurrence of ovulation was assessed by ultrasonography.).; Endometrial thickness and menstrual cycle length were measured in two cycles, cycle 1 for baseline and cycle 2 for treatment in this parallel design study (n=56).
  - When ulipristal acetate (unmicronized capsule) was given in early luteal phase (Table 4),
    - endometrial thickness reduced;
    - menstrual cycle length did not change (no statistical difference).

Table 4. Effect of ulipristal acetate (unmicronized capsule) when it was given in early luteal phase; HRA2914-506

	Endometrial thickness on 4 – 6 days after dosing , mm (mean ± SD)	Mean menstrual cycle length (pre- vs. post-treatment), day

Placebo (n=15)	+1.3 ± 2.3	28.3 vs. 29.6
10 mg (n=13), 50 mg (n=14), and 100 mg (n=14) unmicronized capsule (Data for each dose is not available).	-0.6 ± 2.2	27.8 vs. 28.2

*Baseline endometrial thickness and mean menstrual cycle length were measured in cycle 1; Treatment effect was measured in cycle 2.

- Mid-luteal phase (HRA2914-503; placebo, 1, 10, 50, 100, and 200 mg unmicronized capsule): Mid-luteal phase was defined as 6 – 8 days after LH surge in this parallel design study (n=36).
  - When ulipristal acetate (unmicronized capsule) was given in mid-luteal phase (Table 5),
    - no significant effect on lengths of luteal phase was observed at doses up to 100 mg;
    - high dose (200 mg) ulipristal acetate caused early endometrial bleeding with shorter length of luteal phase which may have been resulted from its anti-progesterone activity.

Table 5. Effect of ulipristal acetate (unmicronized capsule) when it was given in mid-luteal phase; HRA2914-503

	Lengths of luteal phase, day (mean ± SD)	Women with early bleeding, n/n
Placebo	13.4 ± 0.5	0/5
1 mg unmicronized capsule	13.7 ± 1.0	1/6
10 mg unmicronized capsule	13.5 ± 1.1	2/6
50 mg unmicronized capsule	11.8 ± 1.2	3/6
100 mg unmicronized capsule	13.1 ± 1.2	2/7
200 mg unmicronized capsule	9.7 ± 0.3	6/6

2.1.3 What are the proposed indication, dosage and route of administration?

The proposed indication of ulipristal acetate is the prevention of pregnancy following unprotected intercourse or a known or suspected contraceptive failure, not for routine use as a contraceptive. One tablet of ulipristal acetate can be taken orally as soon as possible within 120 hours (5 days) after unprotected intercourse or a known or suspected contraceptive failure. The tablet can be taken with or without food. Ulipristal acetate can be taken at any time during the menstrual cycle.

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing?

Based on findings from three PD studies (HRA2914-503, HRA2914-505, and HRA2914-506; *See section 2.1.2.*), the sponsor decided that 50 mg unmicronized capsule should be developed as an emergency contraceptive. Subsequently the sponsor conducted study HRA2914-501 to compare the absorption profile of three formulations (10 mg unmicronized capsule, 10 mg micronized capsule, and 10 mg micronized tablet). Based on C_{max} and $AUC_{0-\infty}$ of 10 mg micronized tablet being 95 and 38 % higher, respectively, compared to C_{max} and $AUC_{0-\infty}$ of unmicronized capsule (HRA2914-501), the sponsor estimated that 30 mg (calculation based on C_{max}: 26 mg = 50 mg / 1.95; calculation based on $AUC_{0-\infty}$: 36 mg = 50 mg / 1.38) micronized tablet would achieve similar exposure as 50 mg unmicronized capsule.

<u>HRA2914-501: PK comparison of three preparations of the selective progesterone receptor modulator, ulipristal acetate</u>

- Study objective
  - Primary objective was to explore whether (b) (4) unmicronized ulipristal acetate (R) has reduced bioavailability as evaluated by plasma concentrations compared to micronized ulipristal acetate administered by capsule (T1) or tablet (T2) by using standard PK profiles obtained after administration of the three formulations at the same dose, 10 mg.
- Study design
  - Ten potential subjects underwent a screening visit with physical examination to determine eligibility prior to inclusion in the study and all ten entered the study. One subject was withdrawn after the first treatment period due to an adverse event (hyperthyroidism), so only nine subjects completed the study. Eligible subjects were either admitted to the hospital inpatient unit or reported to the hospital. Under fasting conditions, subjects were randomized according to a cross-over design for the first two treatment (R – T1 or T1 – R) periods; all subjects received the third treatment (T2) during the third period. Washout period between each treatment was at least 7 days.
- Demographics

Parameter (N=9)	Mean (SD)	Range
Age (years)	34 (10.4)	19 - 47
BMI (kg/m^2)	25 (4.2)	17.7- 30.0
Race	5 Caucasian, 2 African Americans, 1 Asian, 1 Multiracial	

- Results
  - Ulipristal acetate (Figure 1, Figure 2, and Table 6)
    - Micronized capsule (T1) vs. unmicronized capsule (R)

- After administration of the micronized capsule, the mean C_{max} and $AUC_{0-\infty}$ of ulipristal acetate was higher by 20 and 40%, respectively, compared to the Reference unmicronized capsule. The median t_{max} of ulipristal acetate for both micronized and unmicronized capsules was similar (1.13 vs. 1.25 hours).

▪ Micronized tablet (T2) vs. unmicronized capsule (R)

- After administration of the micronized tablet, the mean C_{max} and $AUC_{0-\infty}$ of ulipristal acetate was higher by 95 and 38%, respectively, compared to the Reference unmicronized capsule. The median t_{max} of ulipristal acetate was shorter for micronized tablet compared to unmicronized capsule (0.62 vs. 1.25 hours)

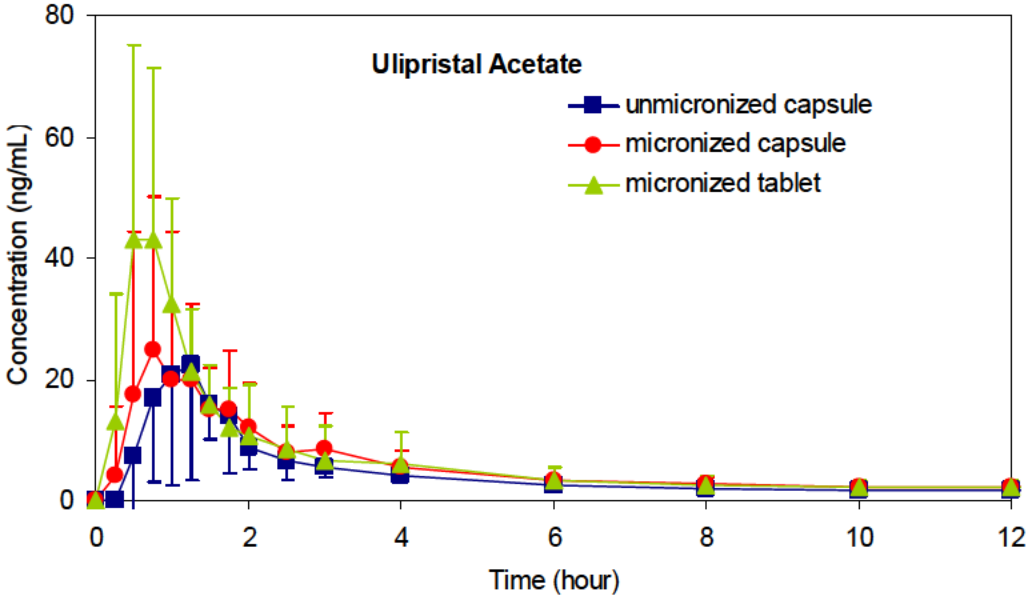


Figure 1. Arithmetic mean (± SD) concentration-time profiles of ulipristal acetate following administration of 10 mg ulipristal acetate (linear scale); HRA2914-501

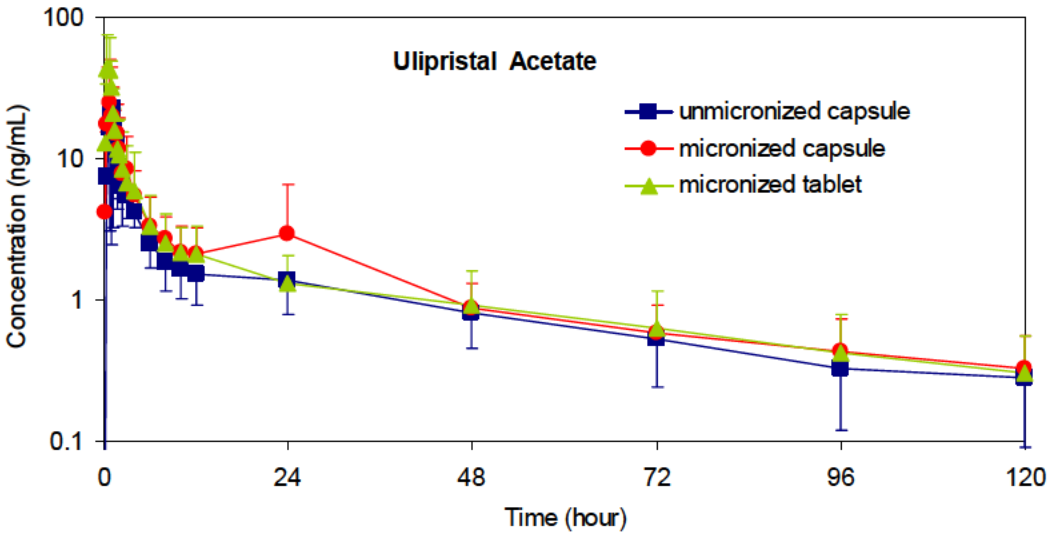


Figure 2. Arithmetic mean (± SD) concentration-time profiles of ulipristal acetate following administration of 10 mg ulipristal acetate (semi-logarithmic scale); HRA2914-501

Table 6. PK parameters of ulipristal acetate following single dose administration of ulipristal acetate 10 mg in three different formulations (unmicronized capsule, micronized capsule, and micronized tablet) to 8 healthy females under fasting conditions; HRA2914-501

Parameter	Mean (CV%)		
	Unmicronized capsule	Micronized capsule	Micronized tablet
C_{max} (ng/mL)	29.1 (59)	35.0 (57)	56.7 (51)
t_{max} (h)*	1.25 (0.50 – 1.50)	1.13 (0.50 – 3.00)	0.62 (0.50 – 2.00)
AUC_{0-t} (ng·h /mL)	123.1 (49)	170.6 (49)	171.8 (50)
$AUC_{0-\infty}$ (ng·h /mL)	138.1 (52)	193.4 (50)	189.9 (53)

*median (range)

- 3877A (Figure 3, Figure 4, and

Table 7)

- Micronized capsule (T1) vs. unmicronized capsule (R)
  - After administration of the micronized capsule, the mean C_{max} of 3877A was higher by 20 % and the mean $AUC_{0-\infty}$ of 3877A was lower by 3% compared to unmicronized capsule. The median t_{max} of ulipristal acetate for both micronized and unmicronized capsules was similar (1.00 vs. 1.25 hours).
- Micronized tablet (T2) vs. unmicronized capsule (R)
  - After administration of the micronized tablet, the mean C_{max} and $AUC_{0-\infty}$ of ulipristal acetate was higher by 92 and 23%, respectively compared to the Reference unmicronized capsule. The median t_{max} of 3877A was shorter for micronized capsule compared to unmicronized capsule (0.75 vs. 1.25 hours)

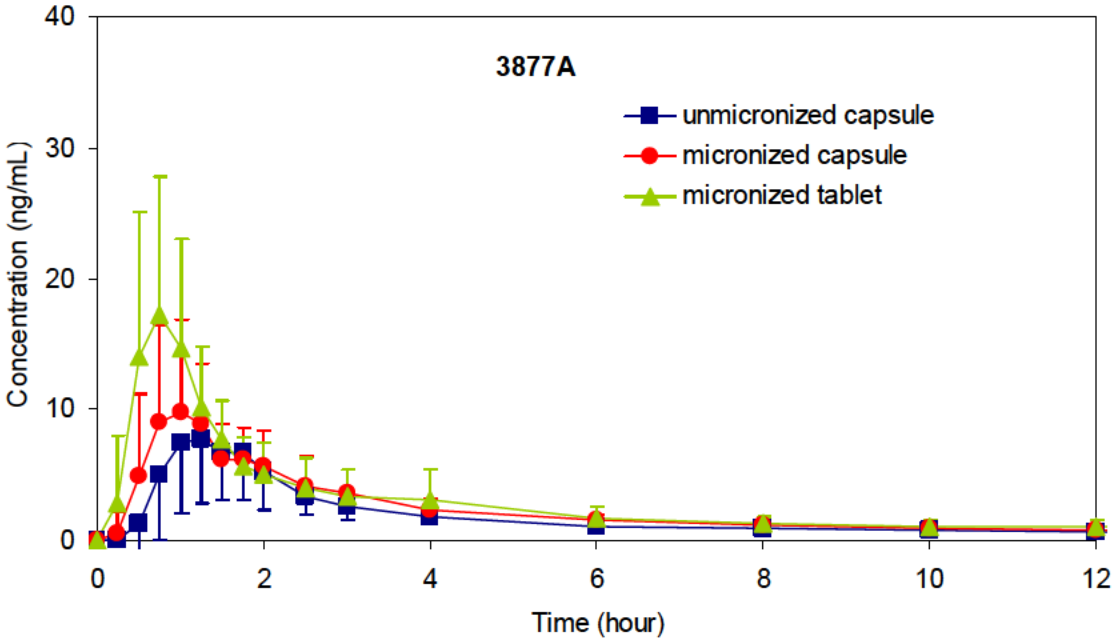


Figure 3. Arithmetic mean (± SD) concentration-time profiles of 3877A following administration of 10 mg ulipristal acetate (linear scale); HRA2914-501

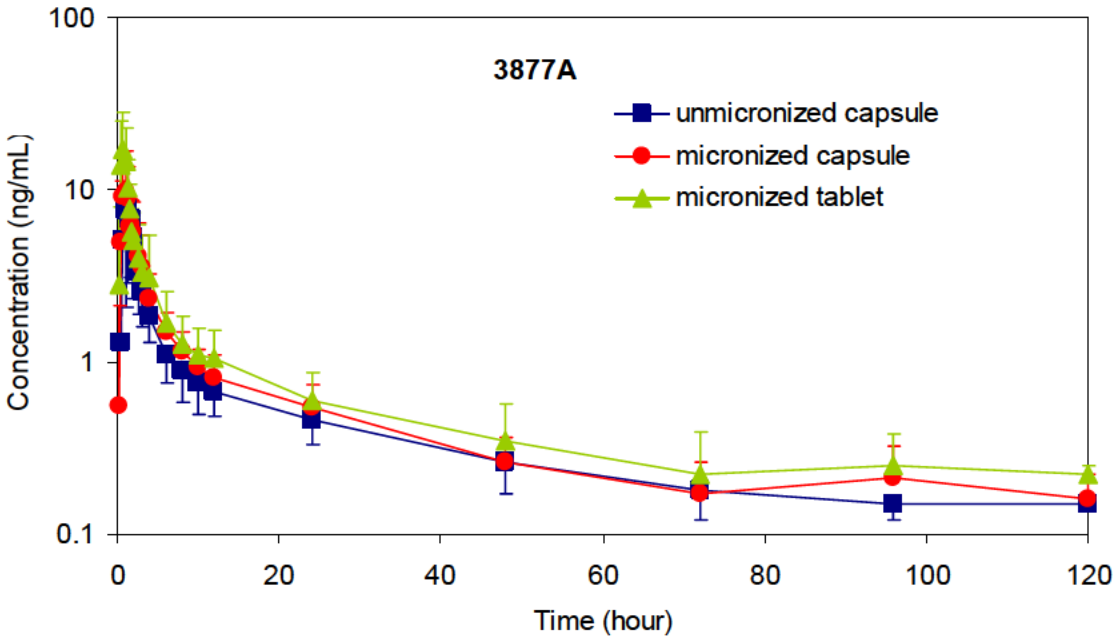


Figure 4. Arithmetic mean (± SD) concentration-time profiles of 3877A following administration of 10 mg ulipristal acetate (semi-logarithmic scale); HRA2914-501

Table 7. PK parameters of 3877A following administration of ulipristal acetate 10 mg in three different formulations (unmicronized capsule, micronized capsule, and micronized tablet) to 8 healthy females under fasting conditions; HRA2914-501

Parameter	Mean (CV%)		
	Unmicronized capsule	Micronized capsule	Micronized tablet
C_{max} (ng/mL)	10.7 (40)	12.8 (40)	20.5 (49)
t_{max} (h)*	1.25 (0.75 – 1.75)	1.00 (0.50 – 2.00)	0.75 (0.50 – 2.00)
AUC_{0-t} (ng·h /mL)	56.5 (59)	54.1 (29)	70.6 (43)
$AUC_{0-\infty}$ (ng·h /mL)	62.8 (55)	61.0 (32)	77.5 (44)

*median (range)

2.2.2 Are the active moieties in the plasma appropriately identified and measured to assess PK parameters?

Yes. Blood samples were withdrawn up to 192 hours for determination of plasma concentration of ulipristal acetate and 3877A.

2.2.3 What are the PK characteristics of the drug and its major metabolite, 3877A?

After administration of a single 30 mg oral dose of ulipristal acetate as a micronized tablet, the drug was absorbed with a median t_{max} of 0.88 hour and a mean C_{max} of 176 ng/mL. Half-life of ulipristal acetate averaged 32.4 hours. The 3877A peaked around 1 hour post-dose with a C_{max} of 68.6 ng/mL, and its half-life averaged 26.6 hours, and its peak concentration averaged 68.6 ng/mL (HRA2914-504).

<u>HRA2914-504: Study of the pharmacokinetic profile of a single 30 mg oral dose of ulipristal acetate in healthy volunteers</u>

- Study objectives
  - To study the PK profile of ulipristal acetate and its principle active metabolite, 3877A after administration of 30 mg single dose micronized tablet.
- Study design
  - This was a single-dose, one-treatment, one-period study under fasting conditions. 20 healthy women were included. The screening visit occurred within 2 weeks before the study drug administration. The subjects signed the informed consent form before any study-related assessment. The subjects entered the clinic on day -1. After an overnight fasting, the subjects were administered one 30-mg ulipristal acetate tablet on day 1. They were discharged from the clinic on the evening of day 1. Blood samples for ulipristal acetate and 3877A assay were taken up to 192 hours post-dose.
- Demographics

Parameter (N=20)	Mean (SD)	Range
Age (years)	25 (6.3)	18 - 35
BMI (kg/m^2)	21.6 (2.0)	19.0 – 25.2
Race	13 Caucasian, 6 African Americans, 1 West Indian	

- Results (Figure 5, Figure 6, and Table 8)
  - Ulipristal acetate and 3877A mean concentration reached a peak within 1 hour of administration. Maximum plasma concentration and exposure of ulipristal acetate was approximately half of the 3877A.

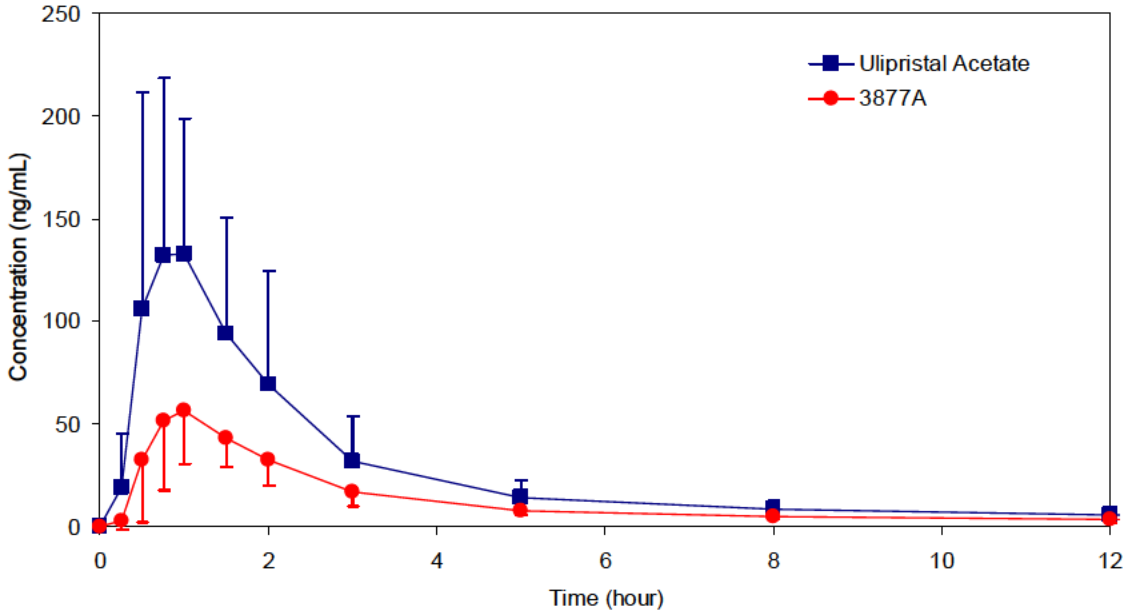


Figure 5. Arithmetic mean (± SD) concentration-time profiles following administration of 30 mg ulipristal acetate (linear scale); HRA2914-504

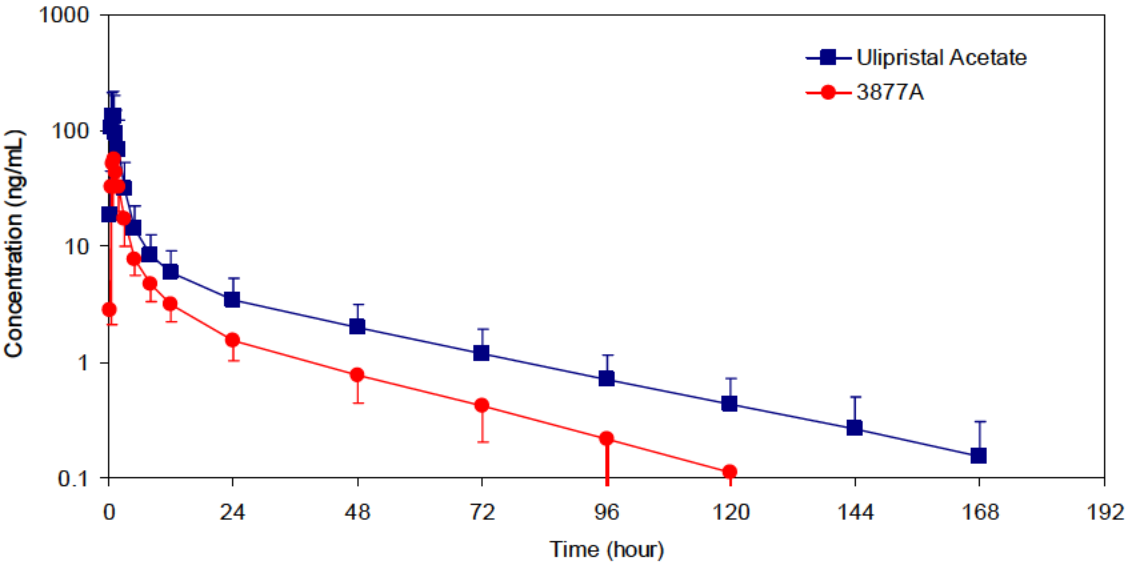


Figure 6. Arithmetic mean (± SD) concentration-time profiles following administration of 30 mg ulipristal acetate (semi-logarithmic scale); HRA2914-504

Table 8. PK parameters of ulipristal acetate and 3877A following single dose administration of ulipristal acetate 30 mg to 20 healthy females under fasting conditions; HRA2914-504

Parameter	Mean (CV%)	
	Ulipristal Acetate	3877A
C_{max} (ng/mL)	176.0 (51)	68.6 (38)
t_{max} (h)*	0.88 (0.50 - 2.00)	1.00 (0.75 - 2.00)
AUC_{0-t} (ng·h/mL)	548.0 (47)	240.0 (24)
$AUC_{0-\infty}$ (ng·h /mL)	556.0 (47)	246.0 (24)
$t_{½}$ (h)	32.4 (20)	26.6 (26)

*median (range)

2.2.3.1 What are the characteristics of drug absorption and elimination?

See section 2.2.3.

2.2.3.2 What are the characteristics of drug distribution?

Ulipristal acetate is shown to be highly bound (> 94 %) to plasma proteins, including, high density lipoprotein, α-acid glycoprotein, and non-esterified fatty acid (HRA2914-427, HRA2914-428, and HRA2914-475).

HRA2914-427: *In vitro* binding of [^{14}C]-ulipristal acetate to human plasma proteins and human blood distribution

- Study design
  - The *in vitro* study was undertaken to evaluate the distribution of ulipristal acetate in blood and binding to human plasma proteins. [^{14}C]-ulipristal acetate in concentrations ranging from 0.007 to 22 μM (3.3 – 10,500 ng/ml) was used in these experiments. Blood used in this experiment was obtained from three healthy female donors, 18-50 years old. Results of binding of ulipristal acetate to blood cells and plasma proteins are presented in Table 9.

Table 9. Relative binding of ulipristal acetate to blood cells and plasma proteins; HRA2914-427

Test system	Ulipristal acetate, µM (ng/ml)	Simulated blood distribution (%)	
Unbound fraction (fu)		1.05	
Bound fraction:		98.95(4.86 + 94.09)	
-To blood cells	0.04-22 (19-10,500 ng/ml)	4.86	
-To plasma proteins	0.02-18.1 (9.5-8,600 ng/ml)	94.09	
% binding to individual plasma proteins			∑ 94.09
-HSA with NEFA (37.31 g/l) (HSA/NEFA=1.44)	0.02-18.1 (9.5-8,600 ng/ml)	15.51	
-AAG (1 g/l)	0.02-15.7 (9.5-7,500 ng/ml)	28.99	
-GG (11.5 g/l)	0.02-9.5 (9.5-4,500 ng/ml)	0.43	
-VLDL (0.5 g/l)	0.007-7.3 (3.3-3,500 ng/ml)	0.47	
-LDL (3 g/l)	0.02-20.7 (9.5-9,800 ng/ml)	19.26	
-HDL (3.5 g/l)	0.02-20.6 (9.5-9,800 ng/ml)	29.44	

*HSA = human serum albumin; NEFA = non-esterified fatty acid; AAG = α-acid glycoprotein; GG: γ-globulins; VLDL = very low density lipoprotein; LDL = low density lipoprotein; HDL = high density lipoprotein

- Results
  - From these results it can be concluded that ulipristal acetate is highly bound in blood and plasma (4.9 % to blood cells and 94.1 % to plasma proteins), with a free fraction of 1.1 %.

HRA2914-428: *In vitro* binding of [^{14}C]-ulipristal acetate to mouse, rat, rabbit, dog, monkey and human plasma (*Only the human data is presented here.*)

- Study design
  - Human plasma was obtained from 3 healthy women donors aged 18-50 years. Equilibrium dialysis was used to determine the amount of plasma protein binding. The concentrations of [^{14}C]-ulipristal acetate tested were 0.03 - 20 µM (14.3 – 9,500 ng/mL).
- Results
  - Mean (SD) protein binding fraction of ulipristal acetate was 98.24 (0.12). The % bound remained constant over the range of ulipristal acetate tested.

HRA2914-475: 3877A - Extent of binding to rat, monkey and human plasma proteins and partitioning between the plasma and cell fraction of human blood (*Only the human data is presented here.*)

- Study design
  - The amount of plasma protein binding at 0.15 and 1.5 µM 3877A was analyzed by LC-MS/MS using equilibrium dialysis methodology. Blood

partitioning analysis was performed and analyzed by LC-MS/MS to obtain the blood-to-plasma ratio.

- Results
  - 3877A was highly bound (96.9%) to plasma proteins. 3877A had a blood cell: plasma ratio of 0.32 showing little binding to red cells compared to moderate and highly bound drugs.

2.2.3.3 What are the characteristics of drug metabolism?

Ulipristal acetate is shown to be metabolized to mono- (3877A) and di- demethylated ulipristal acetate. The data indicated that this metabolism is predominantly mediated by CYP3A4. The mono-demethylated ulipristal acetate appear to exert similar progesterone receptor binding affinity to ulipristal acetate, whereas di-demethylated ulipristal acetate show 10 times weaker progesterone receptor binding affinity compared to ulipristal acetate (HRA2914-429, HRA2914-430, and HRA2914-449).

HRA2914-429: Metabolism of [^{14}C]-ulipristal acetate in microsomes isolated from female mouse, rat, rabbit, dog, monkey and human (*Only the human data is presented here.*)

- Study design
  - Liver microsomes from 10 female donors were purchased for use. A reaction contained 1 mg microsomal protein, 0.8 mM β-NADPH in Tris buffer and 10 µM (4,750 ng/mL) ulipristal acetate. After stopping the reaction with acetonitrile, an aliquot of the sample was analyzed using liquid scintillation to determine recovery of radiolabel. Another aliquot was analyzed by radio-HPLC methodology to determine quantitative and qualitative amounts of parent compound and metabolites produced.
- Results
  - The recoveries from incubations with 10 µM (4,750 ng/mL) ulipristal acetate showed recoveries ranging from 24.3 (incubation for 10 minutes) and 47.9 (incubation for 60 minutes) %. There were two metabolites of ulipristal acetate detected (Table 10). (*Identities of the two metabolites were not determined in this study; Some metabolites (1 to 7) were detected from microsomes of rat, rabbit, dog, monkey, and human.*)

Table 10. Metabolic profile resulting from incubation of 10 µM [^{14}C]-ulipristal acetate in liver microsomes; HRA2914-429

Time (min)	Ulipristal acetate (mean %)	Metabolites (mean %)							Mean % Recovery
		1	2	3	4	5	6	7	
0	99				1.1				101.1
10	75.7				18.4				103.2
60	52.1			19.2	28.2				100.3

HRA2914-430: Identification of the cytochrome P450 enzymes responsible for the *in vitro* metabolism of [^{14}C]-ulipristal acetate and the effect of ulipristal acetate on the activity of specific human cytochrome P450 enzymes

Study HRA2914-430 addresses metabolism as well as drug interaction potential of ulipristal acetate. Therefore, only metabolism part of the study will be presented here. Drug interaction potential part is presented in section 2.4.2.

- Study design
  - Incubations with CYP enzyme inhibitors
    - Experiments to determine the inhibition of ulipristal acetate metabolism were conducted using pooled human liver microsomes. Incubations comprised tris buffer (50 mM, pH 7.4), human liver microsomal protein (1 mg/mL), the selective chemical inhibitors and substrate (Table 11), and [^{14}C]-ulipristal acetate. The total incubation volume was 0.2 mL and the reaction was terminated after 5 minutes.
  - Incubation with cDNA expressed human CYP enzymes
    - Experiments to determine the degree of [14^{C}]-ulipristal acetate metabolism were conducted using microsomes obtained from insect cells transfected with over-expressed human CYP enzymes (supersome). Incubations comprised tris buffer (50 mM, pH 7.4), [14^{C}]-ulipristal acetate (20 µM) and supersome (either CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1 or CYP3A4). The incubation mixture was pre-incubated at 37°C for 5 min prior to initiation with ß-NADPH. Blank incubations contained no supersomes. Blank supersome is microsome obtained from insect cells infected with wild type baculovirus which expressed no enzyme activity. The total incubation volume was 0.2 mL and the reaction was terminated after 5 minutes.

Table 11. Human CYP enzymes tested for inhibition by ulipristal acetate and the enzyme-specific substrates

CYP	Substrate Used / Reaction (µM)	Control Inhibitor (µM)
CYP1A2	phenacetin / O-deethylation (30)	Furafylline (50)
CYP2C9	Tolbutamide / methyl-hydroxylation (100)	Sulfaphenazole (20)
CYP2C19	S-mephenytoin / 4-hydroxylation (80)	Tranylcypromine (100)
CYP2D6	bufuralol / 1-hydroxylation (10)	Quinidine (3)
CYP2E1	lauric acid / 11-hydroxylation (100)	Disulfiram (200)
CYP3A4	midazolam / 1-hydroxylation (10)	Ketoconazole (3)

- Results

- Incubations with CYP enzyme inhibitors
  - Ulipristal acetate was metabolized to two metabolites designated as M1 and M2 in human liver microsomes. The definitive identification of these metabolites was not carried out in this study. Almost complete inhibition of ulipristal acetate metabolism to M1 and M2 occurred with incubation of CYP3A4 and CYP2E1 inhibitors. Minor inhibition to M1 occurred with CYP1A2 and CYP2D6 inhibitors (Table 12).

Table 12. Effects of selective inhibitors on *in vitro* M1 and M2 metabolite production from [^{14}C]-ulipristal acetate in pooled human liver microsomes; HRA2914-430

CYP Isozyme	Inhibitor	Human liver microsome	
		% Inhibition to M1	% Inhibition to M2
Control (without any inhibitors)		0	0
CYP1A2	furafylline	35.8	0
CYP2A6	8-methoxypsoralen	37.5	0
CYP2C9	sulfaphenazole	15.4	0
CYP2C19	tranylcypromine	13.6	4.15
CYP2D6	quinidine	2.96	6.73
CYP2E1	disulfiram	100	87.8
CYP3A4	ketoconazole	100	82.6

- Incubation with cDNA expressed human CYP enzymes
  - After incubation of ulipristal acetate with supersome expressing CYP3A4, M1 and M2 were produced.
  - The % radioactivity from M2 in supersome expressing CYP1A2, 2A6, 2C9, 2C19, 2D6, 2E1 were similar to control and blank supersome, which implied only CYP3A4 was involved in producing M2 (Table 13).

  Since no CYP2E1 activity was implicated in ulipristal acetate metabolism with supersome expressing CYP2E1, the data observed with disulfiram in Table 12 may have been resulted from lack of selective inhibition of disulfiram in CYP2E1 activity.

Table 13. Metabolism of ulipristal acetate with microsomes expressing each CYP enzyme; HRA2914-430

Supersome	% Radioactivity	
	M1	M2
CYP1A2	nd[1]	1.08
CYP2A6	nd	0.73
CYP2C9	nd	1.00
CYP2C19	nd	1.06
CYP2D6	nd	1.79
CYP2E1	nd	1.16
CYP3A4	1.08	6.55
Control[2]	nd	0.88
Blank supersome[3]	nd	1.27

[1] nd = not detected; [2] Control contained microsomes obtained from insect cells infected with wild type baculovirus; [3]Blank supersome contained no supersome

HRA2914-449: *In vitro* antiprogestational/antiglucocorticoid activity and progestin and glucocorticoid receptor binding of the putative metabolites, synthetic derivatives of ulipristal acetate, and mifepristone

- Study design
  - The relative binding affinities (RBAs) for progesterone receptors (PR) and glucocorticoid receptors (GR) of the mono- and di-demethylated metabolites of ulipristal acetate, mifepristone, and mono-demethylated mifepristone was determined. Competitive binding assays for steroid hormone receptors were performed using cytosolic preparations from tissues or cells. Cytosols containing PR or GR were prepared from uterus or thymus, respectively, of rabbits. Recombinant human PR-A or PR-B (rhPR-A, rhPR-B) were assayed in cytosolic extracts from insect cells infected with recombinant baculovirus expressing either human PR-A or human PR-B.
- Results
  - Table 14 summarizes the EC50 and relative binding affinities of these compounds for rhPR-A, rhPR-B, rabbit uterine PR and rabbit thymic GR. Mifepristone, ulipristal acetate, and their mono-demethylated metabolites bound with high affinity to rhPR-A, rhPR-B, and rabbit uterine PR. RBAs for rhPR-A, rhPR-B and rabbit uterine PR of di-demethylated ulipristal acetate were lower than ulipristal acetate and mono-demethylated ulipristal acetate. Mifepristone and its mono-demethylated metabolite showed the highest affinity for rabbit thymic GR, whereas di-demethylated ulipristal acetate showed the lowest affinity.

Table 14. Binding of antiprogestins (mifepristone and ulipristal acetate) and its metabolites to progestin and glucocorticoid receptors

compound	rhPR-B		rhPR-A		Rabbit uterine PR		Rabbit thymic GR	
	EC50 (nM)	RBA[a]	EC50 (nM)	RBA	EC50 (nM)	RBA	EC50 (nM)	RBA[b] (%)

		(%)		(%)		(%)		
Progesterone	8.0 ± 0.3	100	7.7 ± 0.8	100	11.6 ± 0.4	100	-	-
Dexamethasone	-	-	-	-	-	-	8.2 ± 0.4	100
Mifepristone	9.5 ± 0.9	82	10.6 ± 1.3	84	11.5 ± 0.9	99	9.1 ± 0.8	88
Mono-demethylated mifepristone	9.7 ± 1.3	76	11.9 ± 1.3	70	7.7 ± 0.5	132	6.7 ± 0.7	105
Ulipristal acetate	7.7 ± 0.5	99	8.5 ± 0.6	101	13.6 ± 0.6	85	15.4 ± 1.3	53
Mono-demethylated ulipristal acetate	8.8 ± 0.2	78	11.6 ± 1.0	74	11.8 ± 0.9	101	14.7 ± 0.8	55
Di-demethylated ulipristal acetate	83.2 ± 11.9	9	108.5 ± 8.1	8	17.5 ± 2.5	60	73.9 ± 10.3	11

[a]RBA: relative binding affinity = EC50 progesterone / EC50 test compound x 100
[b]RBA: relative binding affinity = EC50 dexamethasone / EC50 test compound x 100

2.3 Intrinsic factors

2.3.1 Does race influence the PK of ulipristal acetate?

No definite PK study was conducted to study the potential effect of race/ethnicity. However, cross study comparisons of PK data from Asians, Caucasians, and African Americans indicate that the exposure of ulipristal acetate and 3877A may be higher in Asians.

The single dose PK data are available from 3 studies (HRA2914-504, HRA2914-512, and HRA2914-516). HRA2914-516 was conducted in Asians only, whereas two other studies (HRA2914-504 and HRA2914-512) were conducted in mostly Caucasians and African Americans (Table 15). Based on a cross study comparison, overall exposure (C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$) of both ulipristal acetate and 3877A from study HRA2914-516 is approximately doubled compared to those from studies HRA2914-504 and HRA2914-512 (Table 16). Since there were no notable differences other than race in these studies which may have contributed to the PK differences, they suggest that exposure of ulipristal acetate and 3877A may be higher in Asians.
See sections 2.2.3 (for HRA2914-504), and 2.4.1 (for HRA2914-512), and 2.1.1 (for HRA2914-516) for detailed information.

There were two phase 3 clinical studies (HRA2914-509 and HRA2914-513) evaluating the safety and efficacy of ulipristal acetate. The race/ethnicity compositions for both study population and pregnancies observed were comparable (Table 17). Therefore, there was no effect of race/ethnicity on the efficacy of ulipristal acetate was observed.

Table 15. Comparison of demographics in three studies; HRA2914-504, HRA2914-512, and HRA2914-516

HRA2914-504		
Parameter (N=20)	Mean (SD)	Range
Age (years)	25 (6.3)	18 - 35

BMI (kg/m^2)	21.6 (2.0)	19.0 – 25.2
Race	13 Caucasian, 6 African Americans, 1 West Indian	
HRA2914-512		
Parameter (N=19)	Mean (SD)	Range
Age (years)	28 (5.2)	19 - 35
BMI (kg/m^2)	22.2 (2.1)	19.0 – 24.9
Race	13 Caucasians, 4 African Americans , 1 Asian, 1 Mauritian	
HRA2914-516		
Parameter (N=53)	Mean (SD)	Range
Age (years)	29 (3.9)	20 – 37
BMI (kg/m^2)	21.5 (2.0)	18.5 – 26.2
Race	53 Asian	

Table 16. Comparison of PK parameters in three studies; HRA2914-504, HRA2914-512, and HRA2914-516

HRA 2914-504		
Parameter	Mean (CV%)	
	Ulipristal Acetate	3877A
C_{max} (ng/mL)	176.0 (51)	68.6 (38)
t_{max} (h)*	0.88 (0.50 - 2.00)	1.00 (0.75 - 2.00)
AUC_{0-t} (ng·h/mL)	548.0 (47)	240.0 (24)
$AUC_{0-\infty}$ (ng·h /mL)	556.0 (47)	246.0 (24)
$t_{½}$ (h)	32.4 (20)	26.6 (26)
HRA2914-512		
Parameter	Mean (CV%)	
	Ulipristal Acetate	3877A
C_{max} (ng/mL)	173 (40)	86.5 (35)
t_{max} (h)*	0.75 (0.50 – 1.50)	0.75 (0.50 – 1.50)
AUC_{0-t} (ng·h/mL)	467 (52)	244 (34)
$AUC_{0-\infty}$ (ng·h /mL)	474 (54)	265 (32)
$t_{½}$ (h)	37.2 (19)	30.0 (25)
HRA2914-516		
Parameter	Mean (CV%)	
	Ulipristal Acetate	3877A
C_{max} (ng/mL)	315.7 (35)	118.5 (33)
t_{max} (h)*	1059.4 (46)	497.7 (34)
AUC_{0-t} (ng·h/mL)	1098.7 (49)	515.0 (35)
$AUC_{0-\infty}$ (ng·h /mL)	0.75 (0.50 – 3.00)	1.00 (0.75 – 3.00)
$t_{½}$ (h)	42.5 (26)	41.9 (48)

* Data presented as median (range)

Table 17. Comparison of study subjects and subjects who got pregnant in phase 3 clinical studies - 1; HRA2914-509 and HRA2914-513

		HRA2914-509		HRA2914-513	
		Study subjects (n=1533, ITT)	Pregnant subjects (n=27, FDA efficacy)	Study subjects (n=1104, ITT)	Pregnant subjects (n=16, FDA efficacy)
Age (years)		24.4 ± 6.1	23.9 ± 5.2	24.5 ± 6.1	24.4 ± 2.6
BMI (kg/m^2)		25.3 ± 6.2	25.1 ± 5.2	25.3 ± 5.9	20.0 ± 14.2
Race, % (n)	Caucasian	60.3 (921)	66.7 (18)	72.8 (804)	75.0 (12)
	African American	21.5 (328)	22.2 (6)	19.0 (210)	25.0 (4)
	Asian	2.3 (35)	3.7 (1)	1.2 (13)	0 (0)
	Other	13.9 (244)	7.4 (2)	7.0 (77)	0 (0)
Food intake, % (n)	Full meal	22.0 (272)*	14.8 (4)	48.3 (533)	31.3 (5)
	Snack	11.6 (143)*	18.5 (5)	34.8 (384)	50 (8)
	No data	66.4 (821)*	66.7 (18)	16.9 (186)	18.8 (3)

*Study subjects for food intake in study HRA2914-509 is from mITT (n = 1241).

Table 18. Comparison of study subjects and subjects who got pregnant in phase 3 clinical studies – 2; HRA2914-509 and HRA2914-513

		Pooled FDA efficacy (HRA2914-509 & HRA2914-513); n = 2182	Pooled pregnancy (HRA2914-509 & HRA2914-513); n=43
Age (years), % (n)	< 18	1.6 (34)	0 (0)
	18 – 35	98.4 (2,148)	100 (43)
BMI (kg/m^2), %, (n)	< 25	60.9 (1,328)	55.8 (24)
	25 – 30	23.1 (504)	18.6 (8)
	> 30	16.0 (350)	25.6 (11)

2.3.2 Does body weight /BMI influence the PK of ulipristal acetate?

There was a trend of decreasing exposure of ulipristal acetate with increasing BMI (19 – 25; HRA2914 504 and HRA2914-512) which may have contributed to the higher pregnancy rate in subjects with BMI > 30 (HRA2914-509 and HRA2914-513).

Subjects with BMI > 30 showed higher pregnancy rate (3.14 %) compared to subjects with BMI ≤ 30 (1.59 % for 25 < BMI ≤ 30, 1.81 % for BMI ≤ 25) in two phase 3 studies (HRA2914-509 and HRA2914-513). In these studies, subjects' BMIs were 25.3 ± 6.2 (HRA2914-509) and 25.3 ± 5.9 (HRA2914-513) kg/m^2. In addition, two phase 1 studies (HRA2914 504 and HRA2914-512) with subjects' BMIs between 19 and 25 showed a visual trend of decreasing exposure (AUC and C_{max}) of ulipristal acetate with increasing BMI, although no statistical significance was observed (for $AUC_{0-\infty}$: $R^2 = 0.0592$, P = 0.1468; for C_{max}: $R^2 = 0.0541$, P = 0.1599; Figure 7). Therefore, this trend (decreasing exposure with increasing BMI) may have contributed to the findings from phase 3 studies in which higher pregnancy rate was observed in subjects with BMI > 30.

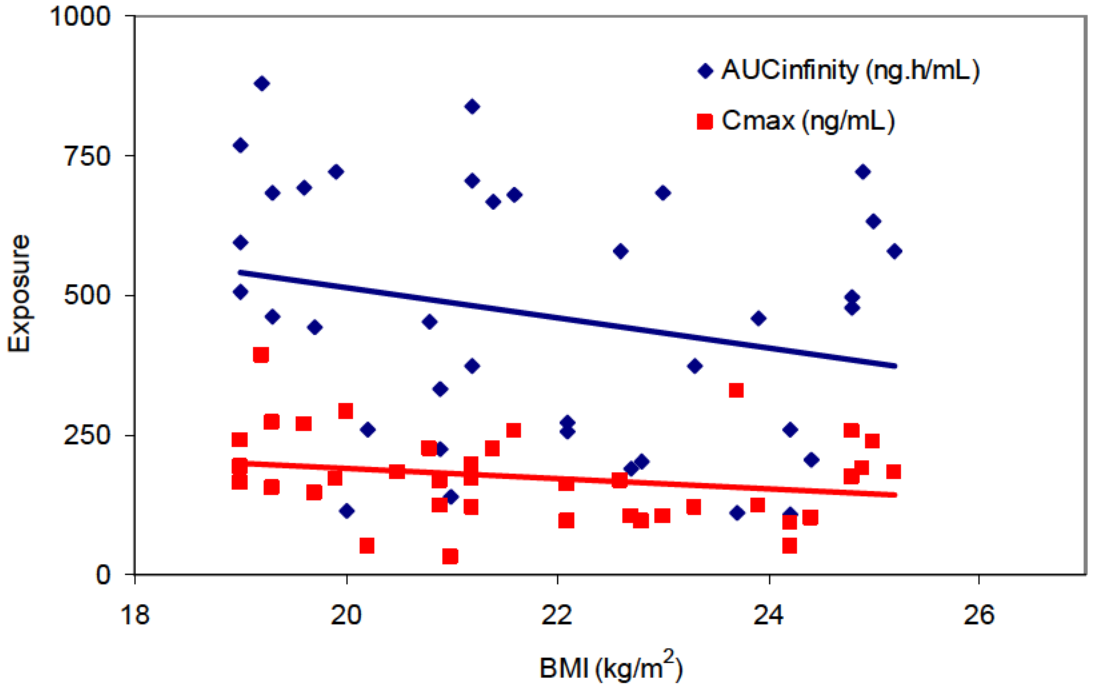


Figure 7. Ulipristal acetate exposure – BMI profiles in two studies, HRA2914-504 and HRA2914-512

2.3.3 Does hepatic disease influence the PK of ulipristal acetate?

No studies were conducted to evaluate the effect of hepatic disease on the PK of ulipristal acetate. However, ulipristal acetate may be poorly metabolized in patients with hepatic impairment.
For drugs intended for single dose administration, a hepatic impairment study will generally not be useful, unless clinical concerns suggest otherwise. (The guidance for industry: PK in patients with impaired hepatic function, FDA, May 2003).

2.3.4 Does renal disease influence the PK of ulipristal acetate?

No studies were conducted to evaluate the effect of renal disease on the PK of ulipristal acetate.
For drugs intended for single dose administration, a renal impairment study will generally not be useful, unless clinical concerns suggest otherwise. (The draft guidance for industry: PK in patients with impaired renal function, FDA, May 2010).

2.4 Extrinsic factors

2.4.1 Does food intake influence the bioavailability of ulipristal acetate?

The status of food intake changed the exposure of ulipristal acetate (decreased C_{max} and increased AUC). However, this finding may not have clinical relevance for efficacy and safety.

Following a single dose administration of ulipristal acetate in with food (high fat/high calorie breakfast), the absorption of ulipristal was reduced as indicated by 40 - 45 % lower C_{max} and delayed t_{max} of about 2 hours for both ulipristal and 3877A (HRA2914-512). However, food intake increased the extent of absorption as indicated by 20 – 25 % higher AUC of ulipristal and 3877A compared to fasting conditions (Table 19).

In the phase 3 clinical studies (HRA2914-509 and HRA2914-513), there was no food restriction, as subjects were dosed as they are in need of emergency contraception. Collection of data on last food intake prior to taking ulipristal acetate was recorded in Case Report Form (CRF). However, food intake status was available only in 33 % of the total study subjects in both studies (HRA2914-509 and HRA2914-513). Based on a limited food intake status data of phase 3 studies, there was no difference in pregnancy rate observed in groups with different food intake status (full meal vs. snack; Table 17). Therefore, ulipristal acetate can be taken regardless of meal.

<u>HRA2914-512: An open, randomized, crossover design study comparing the bioavailability of a single 30 mg oral dose of ulipristal acetate given in fed and fasting conditions in healthy volunteers</u>

- Study objectives
  - to evaluate the impact of concomitant food intake on the relative bioavailability of ulipristal acetate 30 mg tablet
- Study design
  - The study was a randomized two-way cross-over, two treatments, two periods, two sequences, open, single dose study. The study duration was to be at least 36 days per subject (from Day 1 of treatment period 1 to the end-of-study visit) and included two treatment periods separated by a minimum of 21 days (interval between 2 drug administrations), and a follow-up visit at 15 days after the last study drug administration.
- Demographics

Parameter (N=19)	Mean (SD)	Range
Age (years)	28 (5.2)	19 - 35
BMI (kg/m^2)	22.2 (2.1)	19.0 – 24.9
Race	13 Caucasians, 4 African Americans, 1 Asian, 1 Mauritian	

- Results (Figure 8 - Figure 9 and Table 19)
  - Due to the observation of non-linear concentration time profile in semi-logarithmic scale, the terminal half-life (and consequently $AUC_{0-\infty}$) could not be estimated in 1 subject (110) for ulipristal and in 3 subjects (001, 002, 110) for 3877A when dosed under fasting conditions, and in 2 subjects (009 and 110) for both ulipristal and 3877A.

- C_{max} was lower under fed conditions, both for ulipristal (99.2 vs. 173 ng/mL) and for 3877A (54.0 vs. 86.5 ng/mL).
- For both ulipristal and 3877A, the t_{max} was delayed following food intake (medians: 3 vs. 0.75 hour).
- AUCs were slightly increased by food intake, for ulipristal (AUC_{0-t}: 566 vs. 467 ng·h/mL and $AUC_{0-\infty}$: 608 vs. 474 ng·h/mL) as well as for 3877A (AUC_{0-t}: 294 vs. 244 ng·h/mL and $AUC_{0-\infty}$: 310 vs. 265 ng·h/mL).
- The terminal elimination phase started approximately 24 hour post-dose for both treatments. Based on the log-linear mean profiles, the elimination rate seemed similar for both treatments. The terminal elimination half-life averaged around 36 hour for ulipristal and around 30 hour for 3877A, independently of the food conditions.
- In fed conditions, C_{max} fell by approximately 40-45% and time to peak was delayed by approximately 1.25 hours. Administration after a high-fat breakfast resulted in an increase of the extent of absorption by 20-25% in comparison to the administration in fasting conditions.

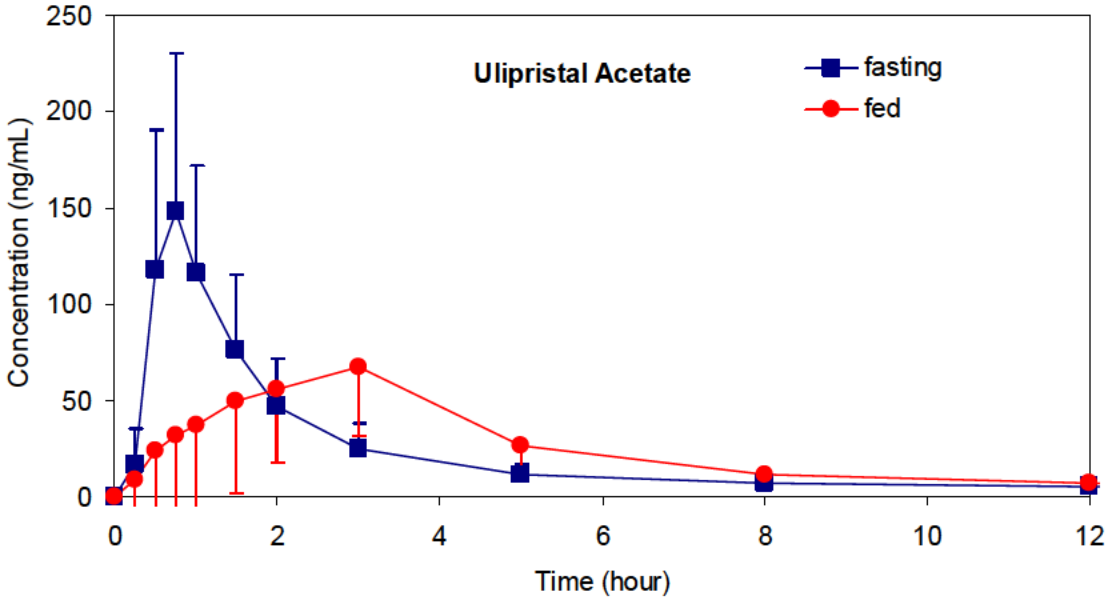


Figure 8. Arithmetic mean (± SD) concentration-time profiles of ulipristal acetate following administration of 30 mg ulipristal acetate under fasting and fed conditions (linear scale); HRA2914-512

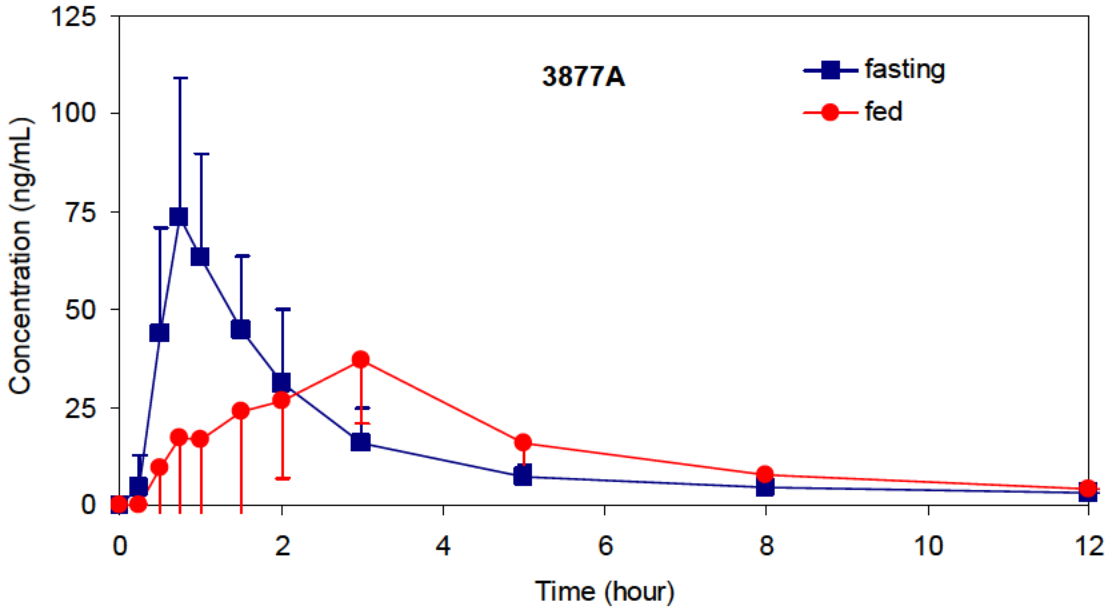


Figure 9. Arithmetic mean (± SD) concentration-time profiles of 3877A following administration of 30 mg ulipristal acetate under fasting and fed conditions (linear scale); HRA2914-512

Table 19. Comparative bioavailability of ulipristal acetate and 3877A following administration of ulipristal acetate 30 mg to 18 healthy females under fasting and fed conditions; HRA2914-512

Parameter	Ulipristal Acetate		90% CI
	fasting	fed	
C_{max} (ng/mL)	173 (40)	99.2 (45)	47.9 – 66.1
t_{max} (h)*	0.75 (0.50 – 1.50)	3.00 (0.50 – 5.00)	-
AUC_{0-t} (ng·h /mL)	467 (52)	566 (50)[a]	112.6 – 135.0
AUC_{inf} (ng·h /mL)	474 (54)[a]	608 (48)[b]	115.7 – 137.6
$t_{1/2}$ (h)	37.2 (19)[a]	36.0 (22)[b]	-
Parameter	3877A		90% CI
	fasting	fed	
C_{max} (ng/mL)	86.5 (35)	54.0 (41)	50.5 – 77.2
t_{max} (h)*	0.75 (0.50 – 1.50)	3.00 (0.50 – 5.00)	-
AUC_{0-t} (ng·h /mL)	244 (34)	294 (32)[a]	111.46 – 132.91
AUC_{inf} (ng·h /mL)	265 (32)[c]	310 (30)[b]	108.09 – 130.42
$t_{1/2}$ (h)	30.0 (25)[c]	28.9 (24)[b]	-

*median (range)
N = 18 except [a] N = 17, [b] N = 16 and [c] N = 15

2.4.2 Are there drug-drug interaction potentials with other drugs?

The effect of other drugs on ulipristal acetate

No *in vivo* drug-drug interaction studies were performed with ulipristal acetate. *In vitro* data indicate that the metabolism of ulipristal acetate is predominantly mediated by

CYP3A4 (*See section 2.2.3.3.*) Concomitant administration of CYP3A4 inhibitors may inhibit the metabolism of ulipristal acetate and cause increased plasma concentration of ulipristal acetate. However, there was no safety concern identified in the phase 3 studies (HRA2914-509 and HRA2914-513). In addition, concomitant administration of CYP3A4 inducers may reduce plasma concentrations of ulipristal acetate and may result in decrease in efficacy. Therefore, *in vivo* drug-drug interaction trial with CYP3A4 inducer needs to be conducted as post marketing requirements.

The effect of ulipristal acetate on other drugs

Based on the findings from three *in vitro* studies (HRA2914-430, HRA2914-476, and HRA2914-477), it is unlikely that the CYP inhibition and CYP induction (CYP1A2 and CYP3A4) by ulipristal acetate and 3877A detected *in vitro* had clinical relevance. Therefore, no further *in vivo* studies to evaluate inhibition or induction of CYP enzyme activity by ulipristal acetate or 3877A are warranted.

HRA2914-430: Identification of the cytochrome P450 enzymes responsible for the *in vitro* metabolism of [^{14}C]-ulipristal acetate and the effect of ulipristal acetate on the activity of specific human cytochrome P450 enzymes

Study HRA2914-430 addresses drug interaction as well as metabolism of ulipristal acetate. Therefore, only drug interaction part of the study will be presented here. Metabolism part is presented in section 2.2.3.3.

- Study design
  - For inhibition of CYP enzyme activity by ulipristal acetate, the human liver microsomes, the CYP-specific substrates (Table 11) at concentration near each Km, and [^{14}C]-ulipristal acetate (10 and 100 µM) were incubated in 50 mM Tris buffer, pH 7.4 at 37°C. All reactions were stopped by the addition of methanol.
- Results
  - Inhibition of CYP enzyme activity by ulipristal acetate
    - CYP activities mediated by CYP2C9, CYP2D6, and CYP3A4 were significantly inhibited by 100 µM ulipristal acetate (Table 20).

<Calculation of [I]/Ki to determine the need for in vivo CYP inhibition study>

1. *Since none of the % inhibition by 10 µM ulipristal acetate was > 50%, IC_{50} of ulipristal acetate for each CYP enzymes was expected to be > 10 µM.*
2. *With substrate concentration near K_m, Ki was calculated to be > IC_{50}/2, which is 5 µM.*
3. *Based on mean C_{max} (176 ng/mL = 0.37 µM) of ulipristal acetate from study HRA2914-512, [I]/Ki = 0.37/5 < 0.1. Therefore, no further in vivo CYP inhibition study with ulipristal acetate was warranted. (The draft guidance for industry: Drug interaction studies, FDA, September 2006).*

Table 20. Inhibition of *in vitro* CYP-mediated Activities by ulipristal acetate in pooled human liver microsomes; HRA2914-430

CYP enzyme	% inhibition relative to CYP specific inhibitor		
	CYP specific inhibitor	Ulipristal acetate (10 μM)	Ulipristal acetate (100 μM)
CYP1A2	83.7	10.1	5.5
CYP2C9	82.8	0.0	50.4
CYP2C19	91.5	0.0	3.0
CYP2D6	83.6	17.9	55.9
CYP2E1	82.3	0.0	10.6
CYP3A4	96.2	31.2	54.0

HRA2914-476: Inhibition of 3877A on CYP Enzyme Activities in Pooled Human Liver Microsomes

- Study design
  - For the pooled CYP cocktail inhibition assay, reactions contained 0.8 mg microsomal protein, 1 mM β-NADPH in 0.1 M KPO4 buffer, pH 7.4 with 5 mM $MgCl_2$, substrate at near K_m concentrations (Table 21) and with or without 4 μM 3877A with a 37°C pre-incubation for 5 min before addition of β-NADPH in triplicate. The reaction was incubated for 20 min. After stopping the reaction with acetonitrile, an aliquot of the sample was analyzed using LC-MS/MS methodology.

  The concentration of 3877A, 4 μM, equated to1,844 ng/mL which was approximately 20 times higher than mean C_{max} of 3877A (86.5 ng.mL) observed in study HRA2914-512.

Table 21. CYP-specific substrates and metabolites

CYP	Substrate Used (μM)	Metabolite
CYP1A2	7-Ethoxyresorufin O-deethylation (0.85)	Resorufin
CYP2A6	Coumarin 7-hydroxylation (3.6)	7-OH coumarin
CYP2C9	Tolbutamide methyl-hydroxylation (166)	OH bupropion
CYP2C19	S-mephenytoin 4-hydroxylation (80)	6α-OH paclitaxel
CYP2D6	Bufuralol 1-hydroxylation (30)	OH tolbutamide
CYP2E1	Chlorzoxazone6-hydroxylation (100)	4'-OH mephenytoin
CYP3A4	Midazolam 1-hydroxylation (10)	1'-OH bufuralol
CYP3A4	Testosterone 6β-hydroxylation (20)	6-OH chlorzoxazone
CYP2B6	Bupropion hydroxylation (100)	1'-OH midazolam
CYP2C8	Paclitaxel 6α -hydroxylation (6)	6-βOH testosterone

- Results
  - 3877A at 4 μM had minimal effect on *in vitro* inhibition of CYP enzyme activities in the cocktail inhibition study with only CYP2C19, CYP2E1, CYP2B6, and CYP2C8 demonstrating inhibition > 10% , and none > 40% (Table 22).

<Calculation of [I]/Ki to determine the need for in vivo CYP inhibition study>

1. *Since none of the % inhibition by 4 µM 3877A was > 50%, IC_{50} of 3877A for each CYP enzymes was expected to be > 4 µM.*
2. *With substrate concentration near K_m, Ki was calculated to be > IC_{50}/2, which is 2 µM.*
3. *Based on mean C_{max} (86.5 ng/mL = 0.18 µM) of 3877A from study HRA2914-512, [I]/Ki = 0.18/ 2 < 0.1. Therefore, no further in vivo CYP inhibition study with 3877A was warranted. (The draft guidance for industry: Drug interaction studies, FDA, September 2006).*

Table 22. Inhibition of 3877A on CYP enzyme activities; HRA2914-476

CYP	Metabolite Formation (nM, mean (SD))		% control activity	% inhibition
	Without 3877A	With 3877A		
CYP1A2	103 (13)	112 (2.9)	109	0
CYP2A6	3270 (164)	3063 (146)	94	6
CYP2C9	1793 (331)	1683 (85)	94	6
CYP2C19	634 (47)	544 (25)	86	14
CYP2D6	871 (77)	799 (45)	92	8
CYP2E1	3097 (338)	2453 (167)	79	21
CYP3A4 (Midazolam)	2200 (506)	2557 (110)	116	0
CYP3A4 (Testosterone)	1550 (296)	1440 (255)	93	7
CYP2B6	411 (58)	257 (10)	63	37
CYP2C8	547 (29)	329 (14)	60	40

<u>HRA2914-477: Induction Effects of ulipristal acetate and 3877A on CYP1A2 and CYP3A4 Activities in Fresh Human Hepatocytes</u>

Based on the findings from liver microsome and supersome expressing CYP enzymes in study HRA2914-430, the sponsor conducted study HRA2914-477 to investigate whether ulipristal acetate and 3877A induced enzyme activity of CYP1A2 and CYP3A4. This reviewer considered enzyme induction study for CYP1A2 in HRA2914-477 unnecessary, since supersome expressing CYP enzyme showed no relevance of CYP1A2 activity for the metabolism of ulipristal acetate in study HRA2914-430. See section 2.2.3.3.

- Study design
  - Fresh human hepatocytes from 2 donors were plated in triplicate at 150,000 cells/cm^2 and incubated with hepatocyte media for 24 h prior to experiments. Subsequently, the cells were treated with ulipristal acetate at 0.5 and 5 µM and 3877A at 0.2 and 2 µM. Positive control CYP inducers were β-naphthoflavone at 10 µM (CYP1A2 inducer) and rifampicin at 50 µM (CYP3A4 inducer).

- CYP1A2 enzyme activity was determined using the O-deethylation reaction of 7-ethoxyresorufin to resorufin.
- CYP3A4 enzyme activity was determined using formation of 6β-hydroxytestosterone from the hydroxylation of testosterone.
- % positive control was calculated as following:
  (activity of test drug treated cells – activity of negative control) × 100 / (activity of positive control – activity of negative control)

- Results
  - β-naphthoflavone (10 μM) increased the formation rate of resorufin by 7- and 14-fold in comparison with those of the vehicle-treated controls, indicating that the CYP1A2 enzyme in the tested hepatocytes was active and inducible. Ulipristal acetate (0.5 and 5 μM) and 3877A (0.2 and 2 μM) did not demonstrate induction effect on CYP1A2 activity at any of the tested concentrations.

Since ulipristal acetate and 3877A were associated with induction of CYP1A2 activity less than 40% of the positive control (β-naphthoflavone), no further in vivo evaluation of ulipristal acetate and 3877A on the induction of CYP1A2 is warranted according to the FDA guidance (Guidance for industry: drug interaction studies, FDA, September 2006).

Table 23. Induction of CYP1A2 Activity by ulipristal acetate and 3877A in Human Hepatocytes; HRA2914-477

Donor	Compound	Treatment	Resorufin Formation (fmol/well/min, mean(SD))	% positive control
1	Control	Solvent	103 (3.7)	0
		β-naphthoflavone (1A2 inducer)	1452 (163)	100
	Ulipristal acetate	0.5 μM	100 (5.7)	-0.2
		5 μM	87 (3.8)	-1.2
	3877A	0.2 μM	93 (5.6)	-0.8
		2 μM	88 (4.6)	-1.1
2	Control	Solvent	77 (4.4)	0
		β-naphthoflavone	545 (29)	100
	Ulipristal acetate	0.5 μM	66 (5.7)	-2.5
		5 μM	75 (6.4)	-0.4
	3877A	0.2 μM	66 (4.4)	-2.5
		2 μM	76 (4.4)	-0.3

- Rifampicin (50 μM) increased the formation rate of 6ß-hydroxytestosterone by 13- and 15-fold in comparison with those of the vehicle-treated controls, indicating that the CYP3A4 enzyme in the tested hepatocytes was active and inducible. Ulipristal acetate and 3877A did not

demonstrate induction effect on CYP3A4 activity at any of the tested concentrations.

Since ulipristal acetate and 3877A were associated with induction of CYP3A4 activity less than 40% of the positive control (rifampin), no further in vivo evaluation of ulipristal acetate and 3877A on the induction of CYP3A4 is warranted according to the FDA guidance (Guidance for industry: drug interaction studies, FDA, September 2006).

Table 24. Induction of CYP3A4 Activity by ulipristal acetate and 3877A in Human Hepatocytes; HRA2914-477

Donor	Compound	Treatment	6ß-hydroxytestosterone Formation (fmol/well/min, mean(SD))	% positive control
1	Control	Solvent	4.6 (1.4)	0
		Rifampin	59 (19)	100
	Ulipristal acetate	0.5 μM	1.4 (0.6)	-5.9
		5 μM	0.5 (0.1)	-7.6
	3877A	0.2 μM	3.3 (0.8)	-2.4
		2 μM	2.6 (0.3)	-3.7
2	Control	Solvent	27 (3.1)	0
		Rifampin	415 (100)	100
	Ulipristal acetate	0.5 μM	18 (1.0)	-2.3
		5 μM	1.9 (0.0)	-6.5
	3877A	0.2 μM	25 (1.4)	-0.7
		2 μM	8.8 (0.3)	-4.8

2.5 General Biopharmaceutics

The particle size distribution specification for 30 mg micronized tablet is as follows:

Particle size (um)	Distribution
(b) (4)	

The phase 3 studies (HRA2914-509 and HRA2914-513) were conducted with 30 mg micronized tablet, manufactured at (b) (4). Subsequently, sponsor decided to manufacture 30 mg micronized tablet at two sites, (b) (4) and Leon Farma in Spain. The bioequivalence between ulipristal acetate tablets manufactured at (b) (4) and Leon Farma (Spain) was established in *in vivo* bridging study (HRA2914-516). *See section 2.1.1 for drug formulation.*

HRA2914-516: A single-dose, open-label, randomized, 2-way crossover bioequivalence study of ulipristal acetate 30 mg tablets manufactured at Leon Farma (Spain) and (b) (4) under fasting conditions in healthy female volunteers

- Study design
  - It was a randomized, two-way crossover, two treatments, two periods, two sequences, single dose study performed in 54 healthy women, 18 - 35 years old and not pregnant. Treatment consisted of a single dose of ulipristal acetate 30 mg tablet from (b) (4) and from Leon Farma, separated by a wash-out period of at least 14 days. Blood sampling for ulipristal acetate and its main metabolite was performed over 168 hours. Fifty-four healthy women provided informed consent and were screened for enrollment into the study and 47 completed the study.
- Disposition of subjects
  - Among the 54 women screened volunteers, who signed informed consent and were enrolled into the study, 53 received at least one dose of the study product (one subject withdrawn her consent). Among the 53 treated subjects, 47 (88.7%) completed all scheduled study visits. Six subjects were withdrawn or discontinued from the study: three due to adverse event and three due to emesis.
    - Subject numbers
      - Emesis: 1018, 1040, and 1041
      - Adverse events
        - Neutropenia: 1029 and 1036
        - Low hemoglobin: 1008
- Demographics

Parameter (N=53)	Mean (SD)	Range
Age (years)	29 (3.9)	20 – 37
BMI (kg/m^2)	21.5 (2.0)	18.5 – 26.2
Race	53 Asian	

- Results
  - Ulipristal acetate (Figure 10, Figure 11, and Table 25)
    - For both the Reference (Cardinal Health) and Test products (Leon Farma), T_{max} occurred between 0.50 and 3.00 hour.
    - The mean C_{max} values of ulipristal acetate for Test and Reference products were similar (geometric mean: 293.4 vs. 315.7 ng/mL, respectively).
    - The mean AUC_{0-t} was similar to $AUC_{0-\infty}$ for the Test and Reference products ($AUC_{0-t}/AUC_{0-\infty} > 0.95$) indicating that the sampling time period was adequate to characterize the PK profile of the doses administered.
    - The results of study regarding ulipristal acetate presented in Table 25 showed that the criteria used to estimate bioequivalence between the Test and Reference products were all fulfilled. Therefore, the Test product, ulipristal acetate 30 mg tablet manufactured at Leon Farma, was bioequivalent to the Reference

product, ulipristal acetate 30 mg tablet manufactured at [redacted].

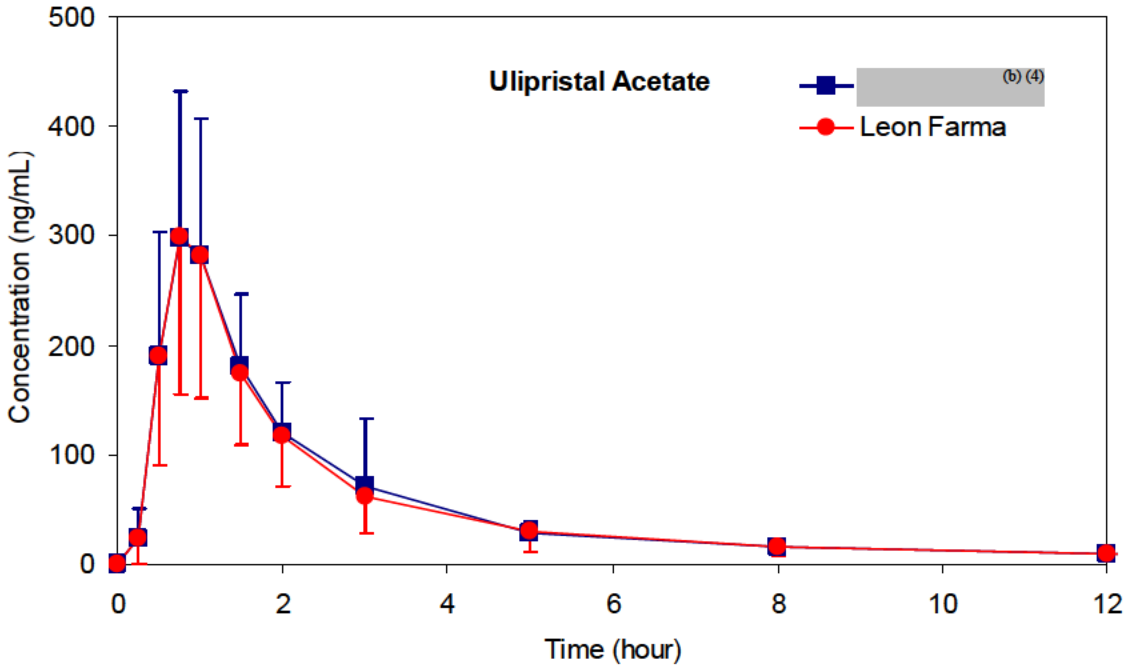


Figure 10. Arithmetic mean (± SD) concentration-time profiles of ulipristal acetate following administration of 30 mg ulipristal acetate (linear scale); HRA2914-516

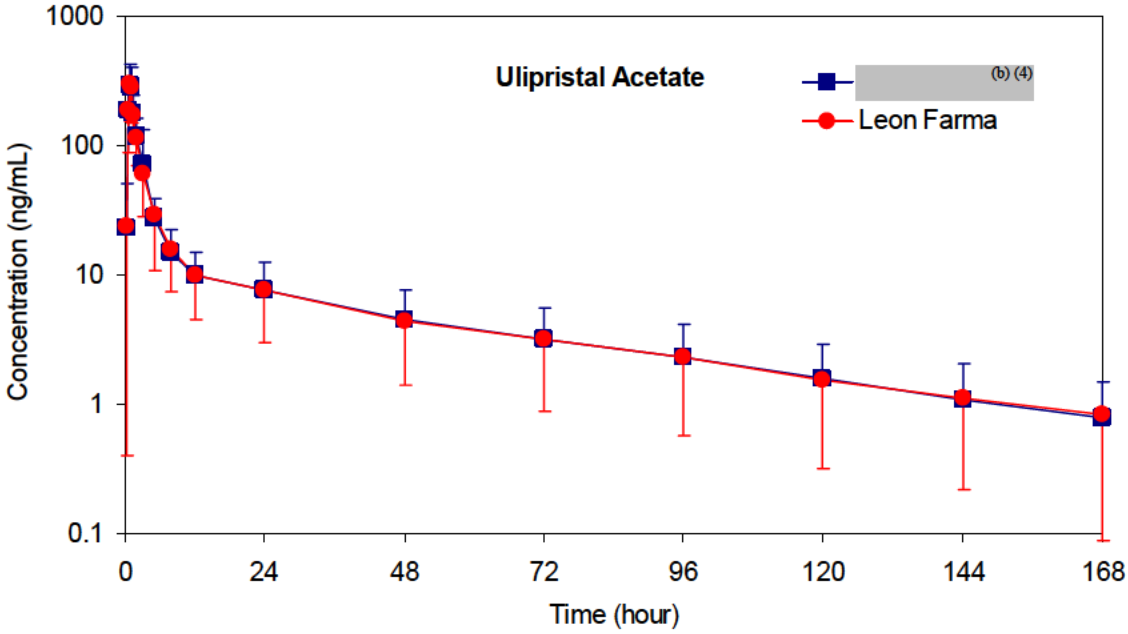


Figure 11. Arithmetic mean (± SD) concentration-time profiles of ulipristal acetate following administration of 30 mg ulipristal acetate (semi-logarithmic scale); HRA2914-516

Table 25. Comparative bioavailability of ulipristal acetate following administration of ulipristal acetate 30 mg manufactured at Leon Farma (Test) and [redacted] (Reference) to 47 healthy females under fasting conditions; HRA2914-516

Parameter	Geometric Mean [CV]		Ratio (Test : Ref)	90% Confidence Interval
	Leon Farma (Test)	[redacted] (Reference)		
C_{max} (ng/mL)	293.4 (44)	315.7 (35)	94.4	86.7 – 102.7
AUC_{0-t} (ng·h /mL)	1041.8 (46)	1059.4 (46)	99.0	94.9 – 103.3
AUC_{inf} (ng·h /mL)	1085.5 (48)	1098.7 (49)	99.4	95.3 – 103.7
t_{max} (h)[a]	0.75 (0.50 – 3.00)	0.75 (0.50 – 3.00)		
$t_{1/2}$ (h)[b]	44.6 (35)	42.5 (26)		

[a] Data presented as median (range)

[b] Data presented as arithmetic mean (CV)

- 3877A (Figure 12, Figure 13, and Table 26)

Although the measurement of the parent drug is generally recommended for bioequivalence study, the sponsor measured both parent drug (ulipristal acetate) and active metabolite (3877A).

- Following a single oral administration of 30 mg tablet of ulipristal acetate manufactured at [redacted] (Reference) and Leon Farma (Test) in 47 female healthy women, the main metabolite of ulipristal acetate, 3877A was measurable in plasma samples collected until 168 hour post-dosing.
- Plasma concentrations of 3877A increased to reach T_{max} between 0.75 and 3.00 hours for the Reference product and between 0.50 and 5.00 hours for the Test product.
- The C_{max} of 3877A was slightly higher in the Reference product than the Test product (geometric mean: 118.5 vs. 110.4 ng/ml).
- The mean AUC_{0-t} was similar to $AUC_{0-\infty}$ for the Test and Reference products ($AUC_{0-t}/AUC_{0-\infty} > 0.95$) indicating that the sampling time period was adequate to characterize the PK profile of the doses administered.
- The results of study regarding 3877A presented in Table 26 showed that the criteria used to estimate bioequivalence between the Test and Reference products were all fulfilled. Therefore, the Test product, ulipristal acetate 30 mg tablet manufactured at Leon Farma, was bioequivalent to the Reference product, ulipristal acetate 30 mg tablet manufactured at [redacted].

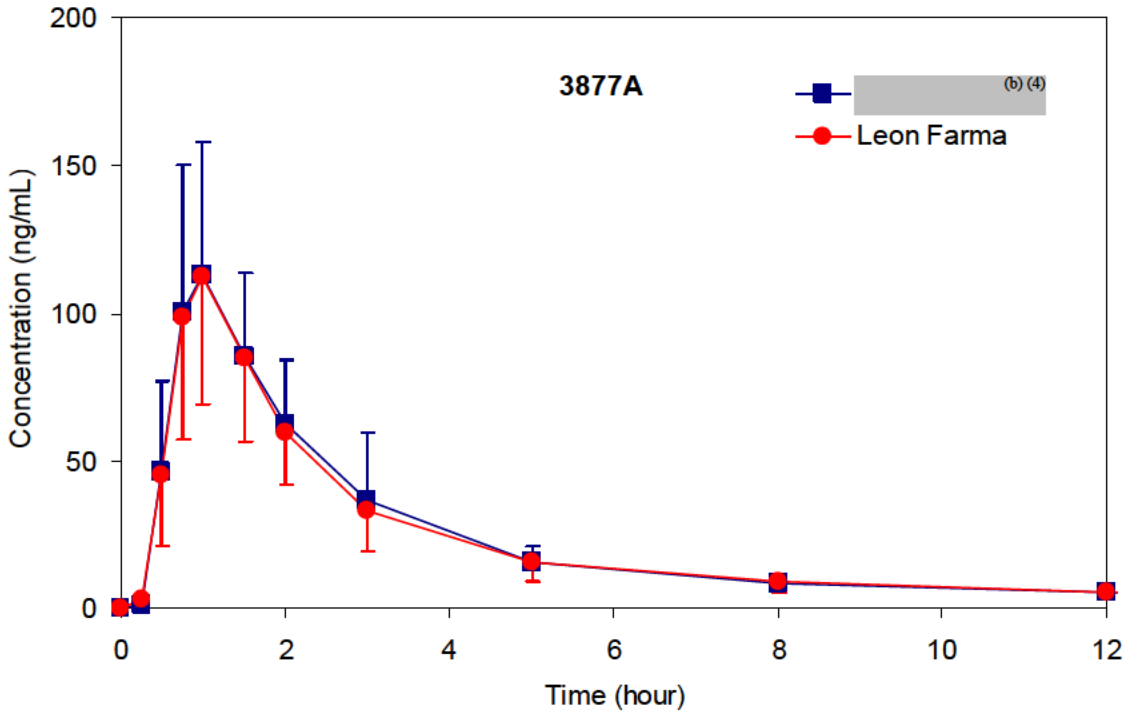


Figure 12. Arithmetic mean (± SD) concentration-time profiles of 3877A following administration of 30 mg ulipristal acetate manufactured at (b) (4) and Leon Farma (linear scale); HRA2914-516

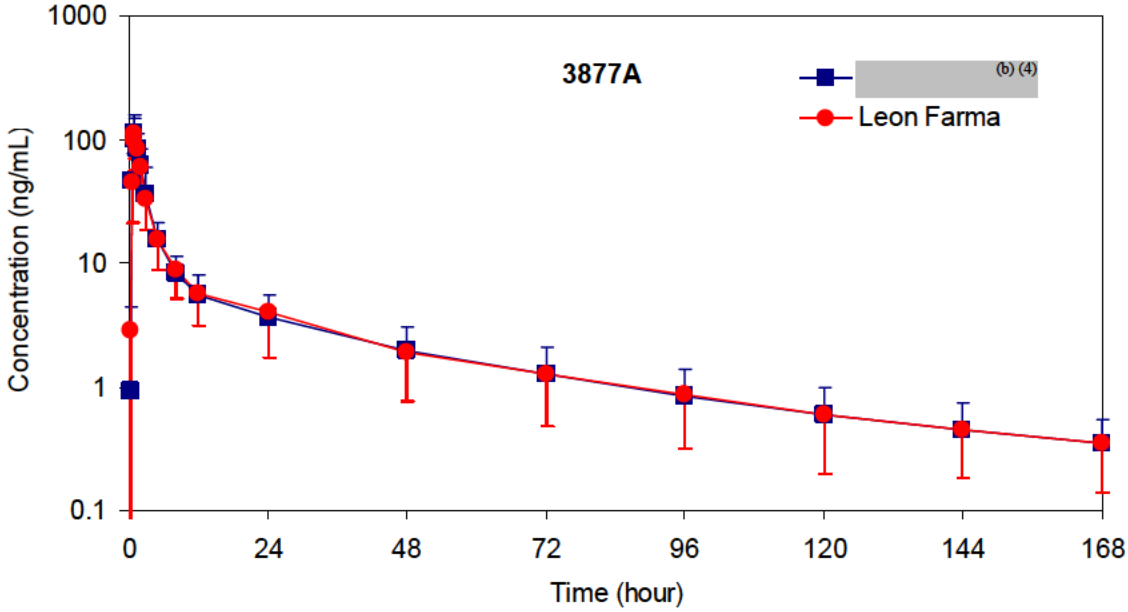


Figure 13. Arithmetic mean (± SD) concentration-time profiles of 3877A following administration of 30 mg ulipristal acetate manufactured at (b) (4) and Leon Farma (semi-logarithmic scale); HRA2914-516

Table 26. Comparative bioavailability of 3877A following administration of ulipristal acetate 30 mg manufactured at Leon Farma (Test) and (b) (4) (Reference) to 47 healthy females under fasting conditions; HRA2914-516

Parameter	Geometric Mean [CV]		Ratio (Test : Ref)	90% Confidence Interval
	Leon Farma (Test)	(b) (4) (Reference)		
C_{max} (ng/mL)	110.4 (35)	118.5 (33)	94.3	87.7 – 101.3
$AUC_{0\text{-}tldc}$ (ng·h /mL)	495.4 (36)	497.7 (34)	100.0	96.1 – 104.0
AUC_{inf} (ng·h /mL)	512.2 (37)	515.0 (35)	100.0	96.1 – 104.0
t_{max} (h)[a]	1.00 (0.50 – 5.00)	1.00 (0.75 – 3.00)		
$t_{1/2}$ (h)[b]	40.1 (28)	41.9 (48)		

[a] Data presented as median (range)

[b] Data presented as arithmetic mean (CV)

2.5.1 Are the clinical trial and the to-be-marketed formulations the same?

Yes. The formulation of ulipristal acetate (30 mg micronized tablet) used in clinical studies is identical to the "to-be-marketed" formulation.

2.6 Analytical Section

- Studies HRA2914-501, HRA2914-504, HRA2914-510, HRA2914-512

Ulipristal acetate and its main metabolite, 3877A, were determined using LC-MS/MS method. The method validation report, CP005404, satisfied the requirements of Bioanalytical Method Validation (Guidance for industry – Bioanalytical method validation, FDA, May 2001).

Component to measure		Ulipristal acetate	3877A
Type of Biological Fluid		Human plasma	Human plasma
Range of Standard Curve		0.1 – 20 ng/mL	0.1 – 20 ng/mL
Linearity (R^2)		0.9955 ± 0.0034	0.9950 ± 0.0030
QC Sample Accuracy	Intra-assay	81.5 – 105.6 %	83.7 – 110.0 %
	Inter-assay	101.3 – 112.0 %	100.0 – 111.8 %
QC Sample Precision	Intra-assay	2.2 – 4.7 %	4.5 – 6.7 %
	Inter-assay	4.5 – 8.8 %	2.8 – 12.1 %
Stability		116 hrs at room temperature; 12.5 months at -6°C; 3 cycles of freezing/thawing	116 hrs at room temperature; 12.5 months at -6°C; 3 cycles of freezing/thawing
Recovery		(b) (4)	(b) (4)

All human (female) samples of studies HRA2914-501, HRA2914-504, HRA2914-510 and HRA2914-512 were analyzed for the content of ulipristal acetate and 3877A according to the validated method validation report, CP005404, as reported in bioanalytical reports, CP035139 (for a study HRA2914-501), CP070186 (for a study HRA2914-504), CP035445 (for a study HRA2914-510), and CP070223 (for a study HRA2914-512).

- Study HRA2914-516

Ulipristal acetate and its main metabolite, 3877A, were determined using LC-MS/MS method. The method validation report, API4000, satisfied the requirements of Bioanalytical Method Validation (Guidance for industry – Bioanalytical method validation, FDA, May 2001).

Component to measure		Ulipristal acetate	3877A
Type of Biological Fluid		Human plasma	Human plasma
Range of Standard Curve		0.1 – 250 ng/mL	0.1 – 100 ng/mL
Linearity (R^2)		0.9952 – 0.9998	0.9958 – 0.9994
QC Sample Accuracy	Intra-assay	85.1 – 113.9 %	84.7 – 97.1 %
	Inter-assay	91.0 – 106.4 %	90.4 – 95.5 %
QC Sample Precision	Intra-assay	1.8 – 15.3 %	1.5 – 11.3 %
	Inter-assay	2.9 – 9.7 %	2.5 – 9.2 %
Stability		9 hrs at room temperature; 66 days at -22 ± 5°C; 3 cycles of freezing/thawing	9 hrs at room temperature; 66 days at -22 ± 5°C; 3 cycles of freezing/thawing
Recovery		(b) (4)	(b) (4)

All human (female) samples of study HRA2914-516 were analyzed for the content of ulipristal acetate and 3877A according to the validated method validation report, API4000, as reported in bioanalytical report, 016-09.

- Studies HRA2914-503 and HRA2914-503b

The studies HRA2914-503 and HRA2914-503b correspond to a scientific publication of a PK/PD study performed by the National Institute of Child Health and Human Development. During this study, radioimmunoassay (RIA) method was used but the sponsor does not have any data other than those published in the article. The sponsor has neither a study-specific analytical report nor a method validation report for the RIA method that was used in these studies.

4 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/

HYUNJIN KIM
07/08/2010

MYONG JIN KIM
07/09/2010

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Concur with PMR