



U.S. Food and Drug Administration

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ella[®]
ulipristal acetate

FDA Reproductive Health Drugs Advisory Committee
June 17, 2010

Introduction

Erin Gainer, PhD, MPH
CEO, HRA Pharma

Agenda

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History of Emergency Contraception

James Trussell, PhD
*Prof. of Economics and Public Affairs
Director, Office of Population
Research, Princeton University*

Mechanism of Action of Emergency Contraception

David Archer, MD
*Prof. of Obstetrics & Gynecology
Director Clinical Research Center
Eastern Virginia Medical School*

Pharmacodynamics and Efficacy of Ulipristal Acetate

Erin Gainer, PhD, MPH

Safety of Ulipristal Acetate

Delphine Lévy, MD
Head of Medical Affairs, HRA Pharma

Benefit/Risk and Conclusions

Erin Gainer, PhD, MPH

Experts Available to the Committee

- ◆ **Diana Blithe, PhD**

Health Scientist Administrator, NICHD

- ◆ **Vivian Brache, Lic.**

Director, Biomedical Research Department, Profamilia, Santo Domingo

- ◆ **Paul Fine, MD**

Prof. of Obstetrics & Gynecology and Urology, Baylor College of Medicine; Medical Director, Planned Parenthood of Houston and Southeast Texas and Louisiana

- ◆ **Vanessa Cullins, MD, MPH**

Vice President for Medical Affairs, Planned Parenthood Federation of America

Ulipristal Acetate 30 mg Tablet

Proposed Indication

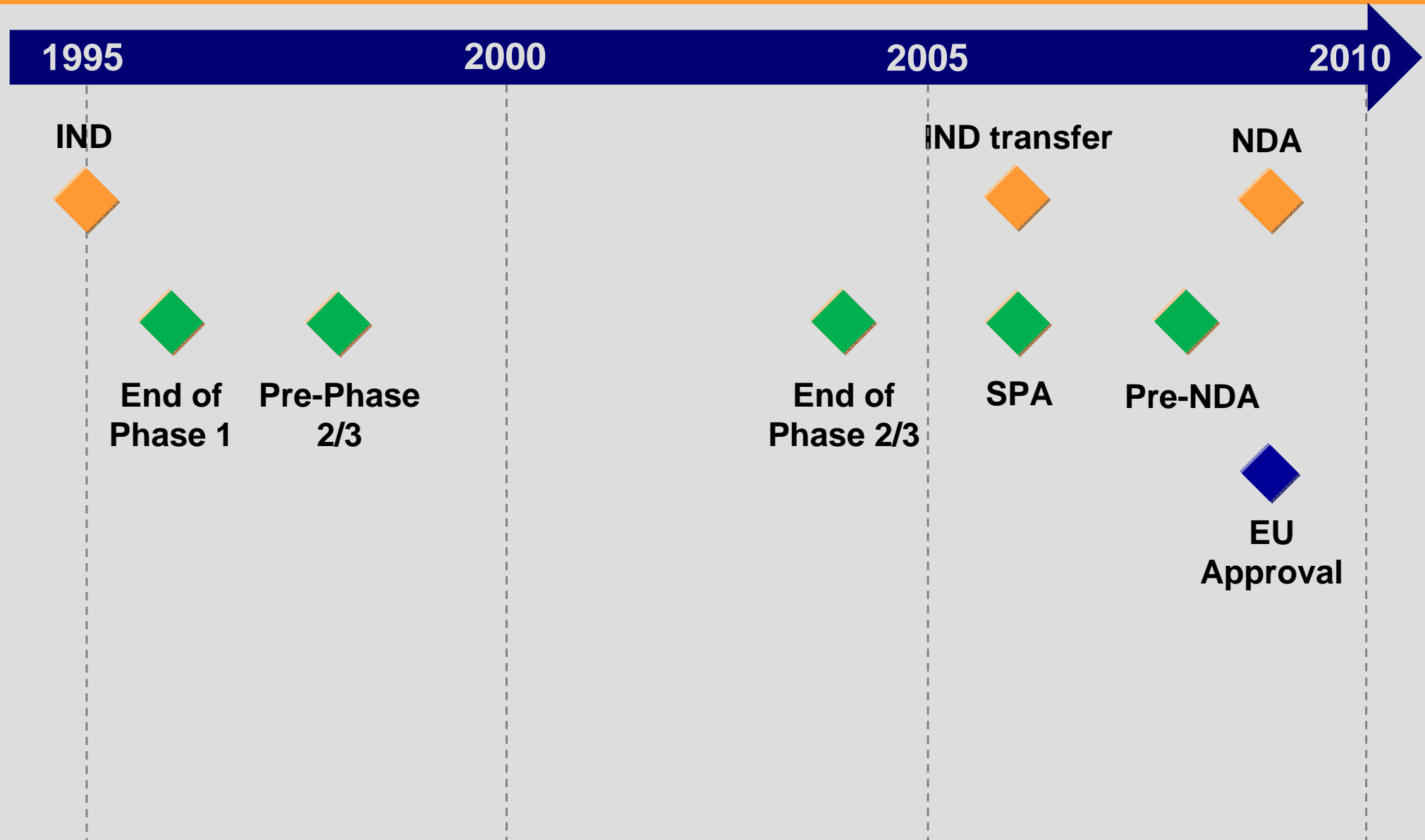
- ◆ Emergency contraception indicated for the prevention of pregnancy following unprotected intercourse or a known or suspected contraceptive failure

Proposed Dosing Regimen

- ◆ One tablet to be taken orally as soon as possible within 120 hours (5 days) after unprotected intercourse or a known or suspected contraceptive failure

Regulatory Background – NDA 22-474

FDA Interactions

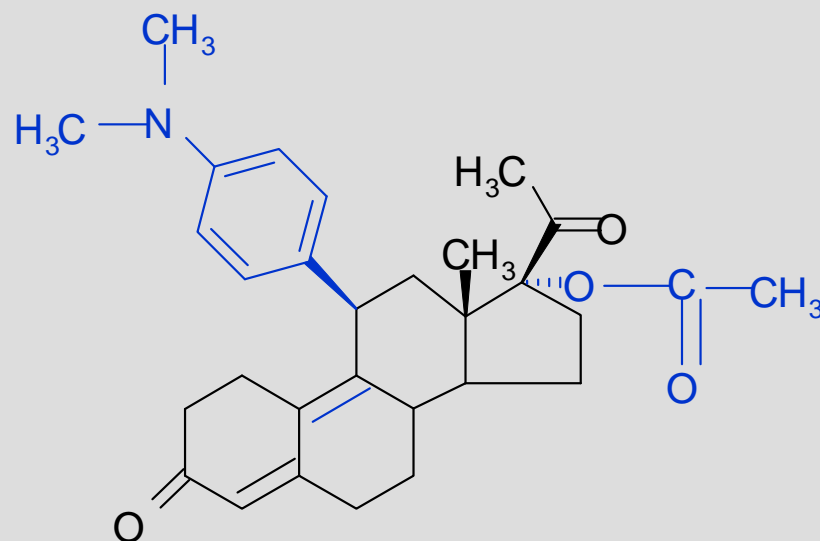


Ulipristal Acetate (UPA)

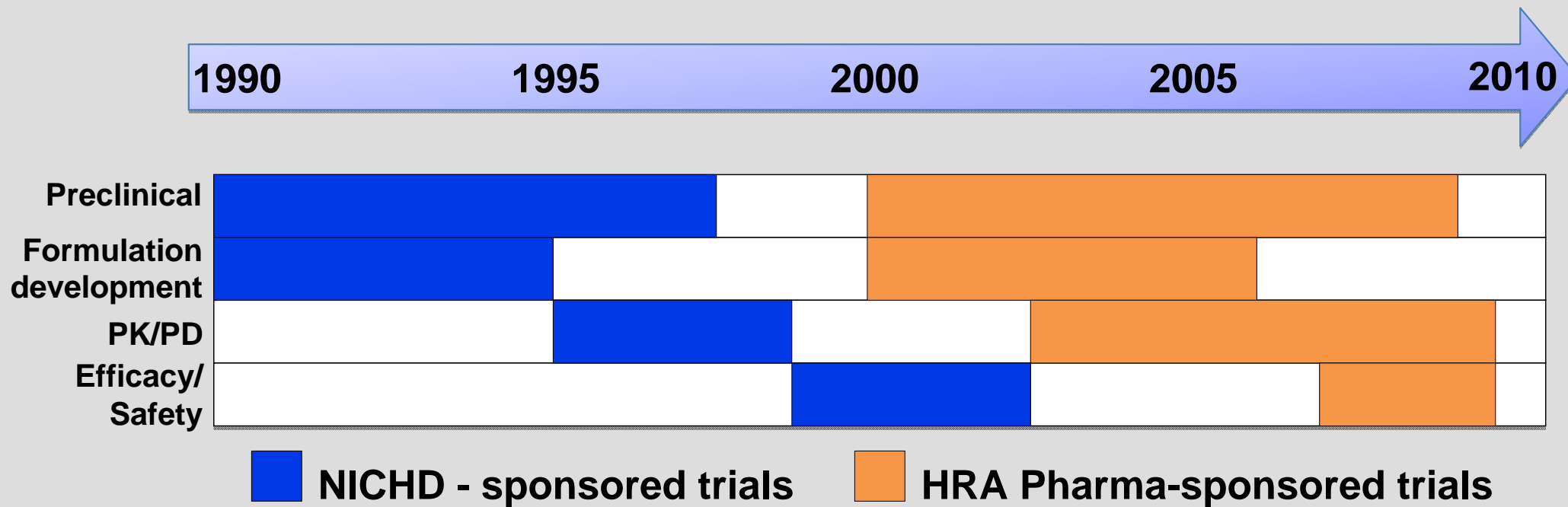
- ◆ New molecular entity
- ◆ First compound in new pharmacological class (“pristal”)
- ◆ Developed by Research Triangle Institute (RTI 3021-012)
- ◆ Initial research conducted by the NICHD (CDB-2914)
- ◆ HRA Pharma identified the compound as a promising target for a next generation emergency contraceptive
 - License from RTI (2000)
 - Collaborative research & development agreement with NICHD (2002)

Ulipristal Acetate

- ◆ Selective progesterone receptor modulator
 - Binds strongly to the progesterone receptor and induces conformational changes
 - Antagonizes the receptor in target tissues (uterus, cervix, ovaries, hypothalamus)



Development of Ulipristal Acetate



Overview

- ◆ Half of the pregnancies that occur in the US are unintended
- ◆ Emergency contraception provides a back-up solution for women who find themselves at risk of unintended pregnancy
- ◆ Ulipristal acetate presents a promising pharmacological profile for emergency contraception
- ◆ Evidence of efficacy from clinical trials of over 4,000 women: ulipristal acetate significantly reduces pregnancy risk
- ◆ Extensive safety database: no specific risks, tolerability profile similar to currently-marketed emergency contraceptives

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Why Are We Here?

“As long as condoms break, inclination and opportunity unexpectedly converge, men rape women, people are so ambivalent about sex that they need to feel ‘swept away,’ and pills are lost or forgotten, we will need morning-after birth control. Our birth control technology is imperfect, and human behavior is imperfect.”

Why Are We Here?

- ◆ Every woman deserves a last chance to prevent pregnancy after unprotected intercourse: > 1 million each day in US ⁽¹⁾
- ◆ An important option for women who have been sexually assaulted; 25,000 become pregnant each year ⁽²⁾

1- Hatcher, et al. *Contraceptive Technology* 19th Revised Edition. New York: Ardent Media, 2007.

2- Holmes, et al. *Am J Obstet Gynecol*. 1996;175:320-325.

Why Are We Here?

- ◆ In actual use, contraceptive failure is common

Method	12-mo failure rate (pregnancies per 100 women)	
	Perfect use	Actual use
Oral contraceptives	0.3	9
Condoms	2	17

When Is Emergency Contraception Indicated?

- ◆ Intercourse without contraception
- ◆ Contraceptive accident
 - Missed pills
 - Slipped or broken condom
 - Unsuccessful withdrawal
- ◆ Sexual assault

Where Did We Start?

- ◆ First reported use in 1964: Amsterdam police brought a 13-yr-old rape survivor to the hospital
- ◆ Attending doctors asked a veterinarian about estrogen dose used for dogs after “unwanted mating”
- ◆ Started to use postcoital estrogen routinely (5 mg ethinyl estradiol for 5 days)
- ◆ By 1975, 55,000 doses used per year in Netherlands

The Yuzpe Regimen

- ◆ Canadian gynecologist Albert Yuzpe wanted an alternative to high-dose estrogen
- ◆ Tried 100 mcg EE and 750 mcg levonorgestrel (2 Ovral pills) for students presenting within 120 hrs of unprotected intercourse
- ◆ Dissatisfied, he next tried 2 doses 12 hrs apart for students presenting within 72 hrs of unprotected intercourse

Yuzpe, et al. *J Reprod Med*. 1974;13:53-58.

Yuzpe, et al. *Fertil Steril*. 1977;28:932-936.

Yuzpe Regimen In US

- ◆ For > 25 yrs, clinicians dispensed cut-up packets of Ovral in the absence of a dedicated EC product
- ◆ FDA held advisory committee meeting in 1996 and published a notice in the Federal Register in 1997 declaring 6 brands of COCs to be safe and effective for use for emergency contraception
- ◆ Preven approved in 1998: 14 yrs after PC4 was approved in UK

Levonorgestrel Alone

- ◆ 750 mcg levonorgestrel was marketed as a postcoital contraceptive (within 1 hr) for women having intercourse infrequently
- ◆ Trials of 2 tablets for use for emergency contraception seemed promising

Levonorgestrel vs Yuzpe

- ◆ In meta-analysis of two randomized trials, women treated with levonorgestrel up to 72 hr after unprotected intercourse
 - Had significantly fewer side effects
 - Had 49% fewer pregnancies

Ho, et al. *Hum Reprod.* 1993;8:389-392.

Task Force on Postovulatory Methods of Fertility Regulation. *Lancet.* 1998;352:428-433.

Raymond, et al. *Contraception.* 2004;69:79-81.

Levonorgestrel In the US

- ◆ **1999: Plan B approved (0.75 mg levonorgestrel taken 0 - 72 hr after unprotected intercourse and a second dose repeated 12 hr later)**
- ◆ **2006: Plan B switched to OTC with age restriction**
- ◆ **2009: Plan B One-Step approved (1.5 mg levonorgestrel taken 0 - 72 hr after unprotected intercourse)**
- ◆ **2009: Next Choice (generic Plan B) approved**

Ulipristal Acetate

- ◆ **Ulipristal acetate is a selective progesterone receptor modulator developed as an emergency contraceptive by NIH**
- ◆ **Marketed since October 2009 as ellaOne in 22 European countries for use for up to 120 hr after unprotected intercourse**
- ◆ **American women would also benefit from this emergency contraceptive option, whose efficacy does not decline with delay in use**

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The Fertile Window

Probability of conception on specific days near the day of ovulation

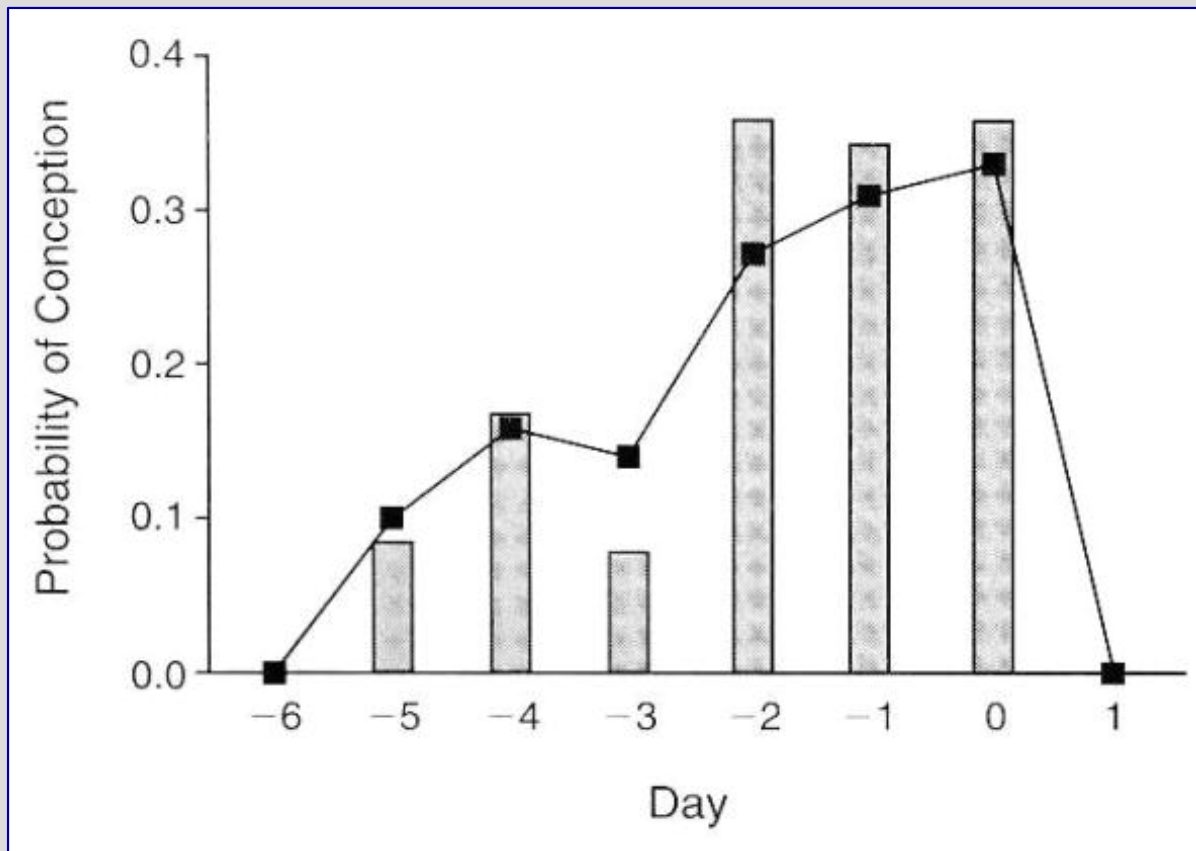


Figure 2 from *Wilcox et al. 1995*

The bars represent probabilities calculated from data on 129 menstrual cycles in which sexual intercourse was recorded to have occurred on only a single day during the 6-day interval ending on the day of ovulation (day 0). The solid line shows daily probabilities based on all 625 cycles, as estimated by the statistical model.

Frequency of Intercourse

Proportion of contracepting women who have intercourse on a given day of the menstrual cycle, relative to the day of ovulation

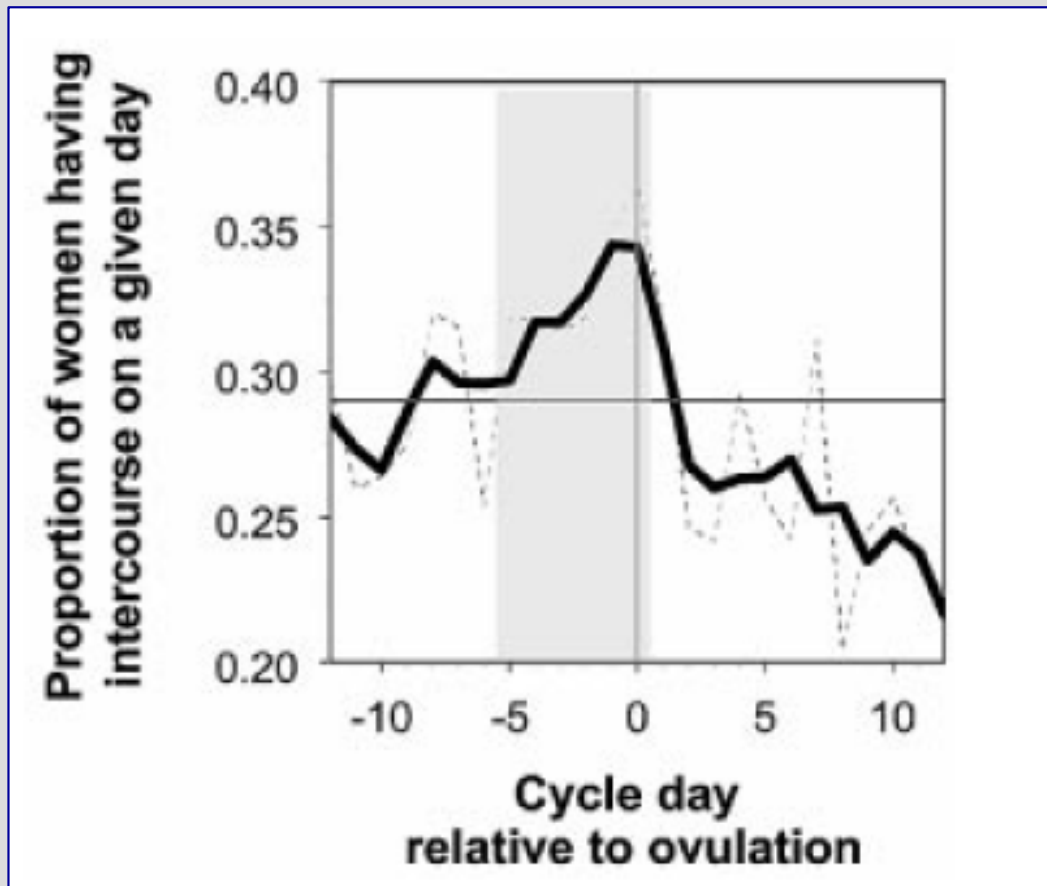
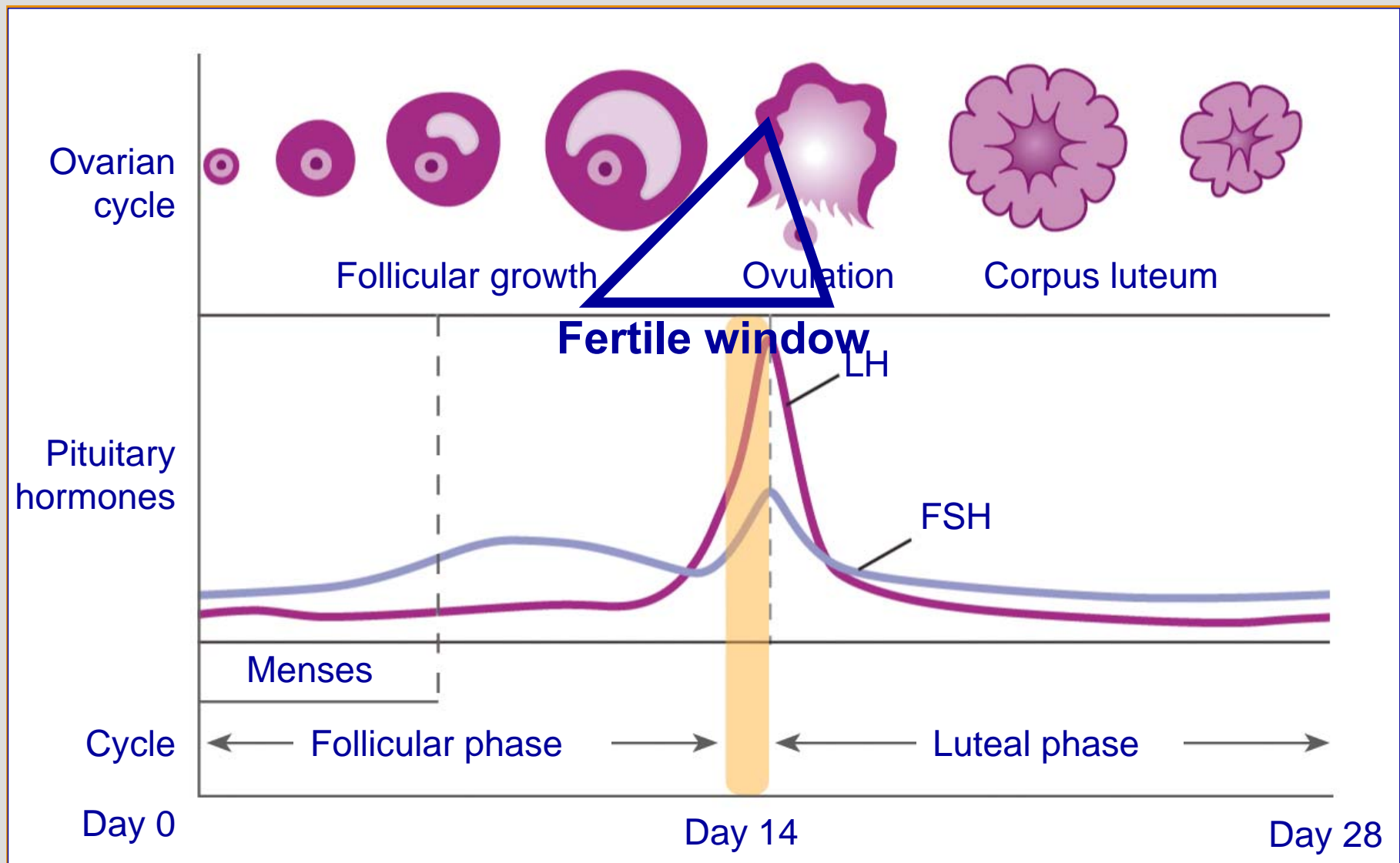


Figure 1 from *Wilcox et al. 2004*

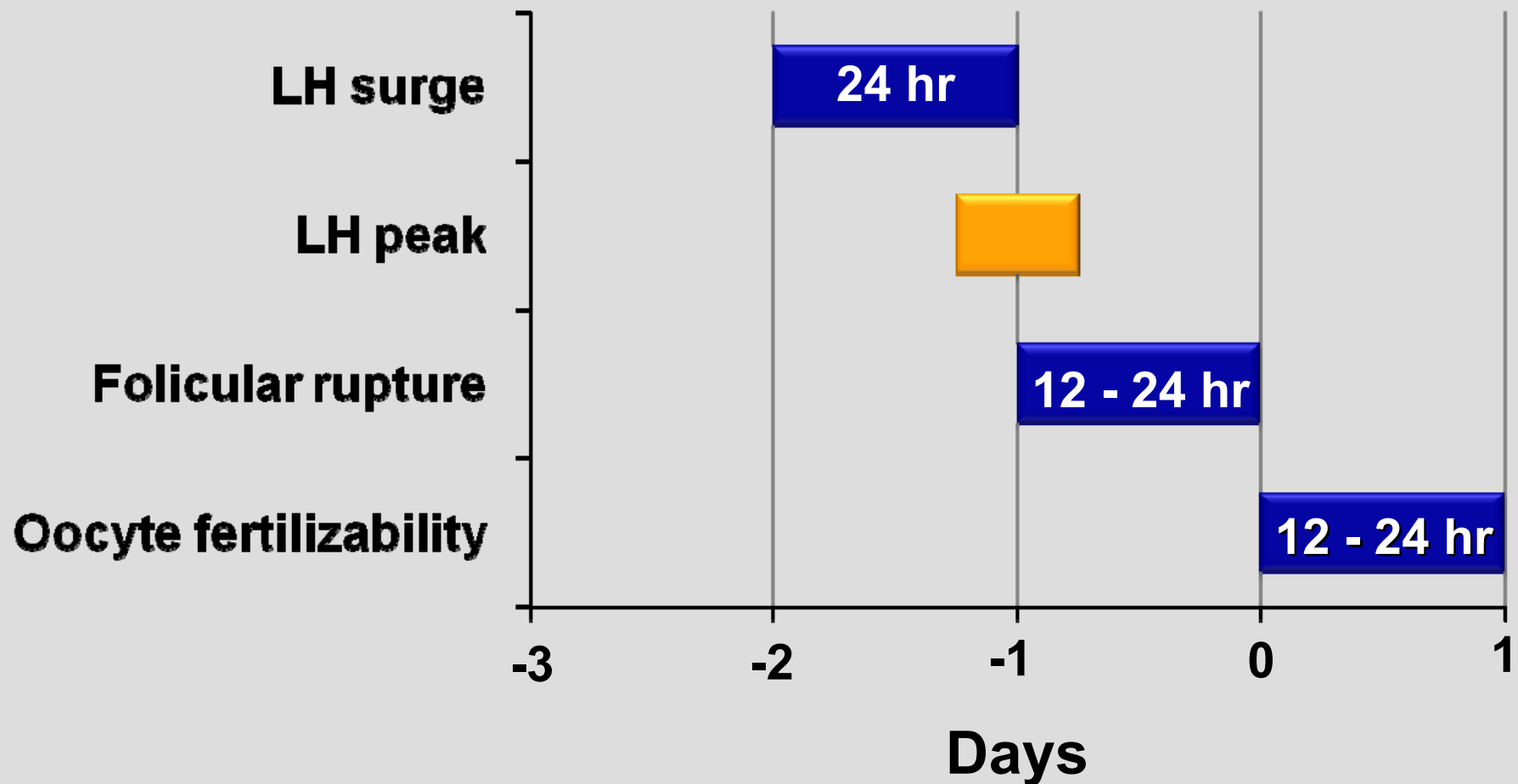
Dashed line shows mean value for each day, while the dark solid line shows the 3-day moving average (each data point representing the mid-point of a 3-day span). The 6% fertile days are shaded, with the day of ovulation (0) marked by the thin vertical line. The intercourse line represents the overall mean frequency of intercourse on non-bleeding days (0.290). n = 68 women, 171 cycles.

Physiology of the Fertile Window



The Fertile Window: Events Around Ovulation

Once leading follicle reaches 16 - 20 mm



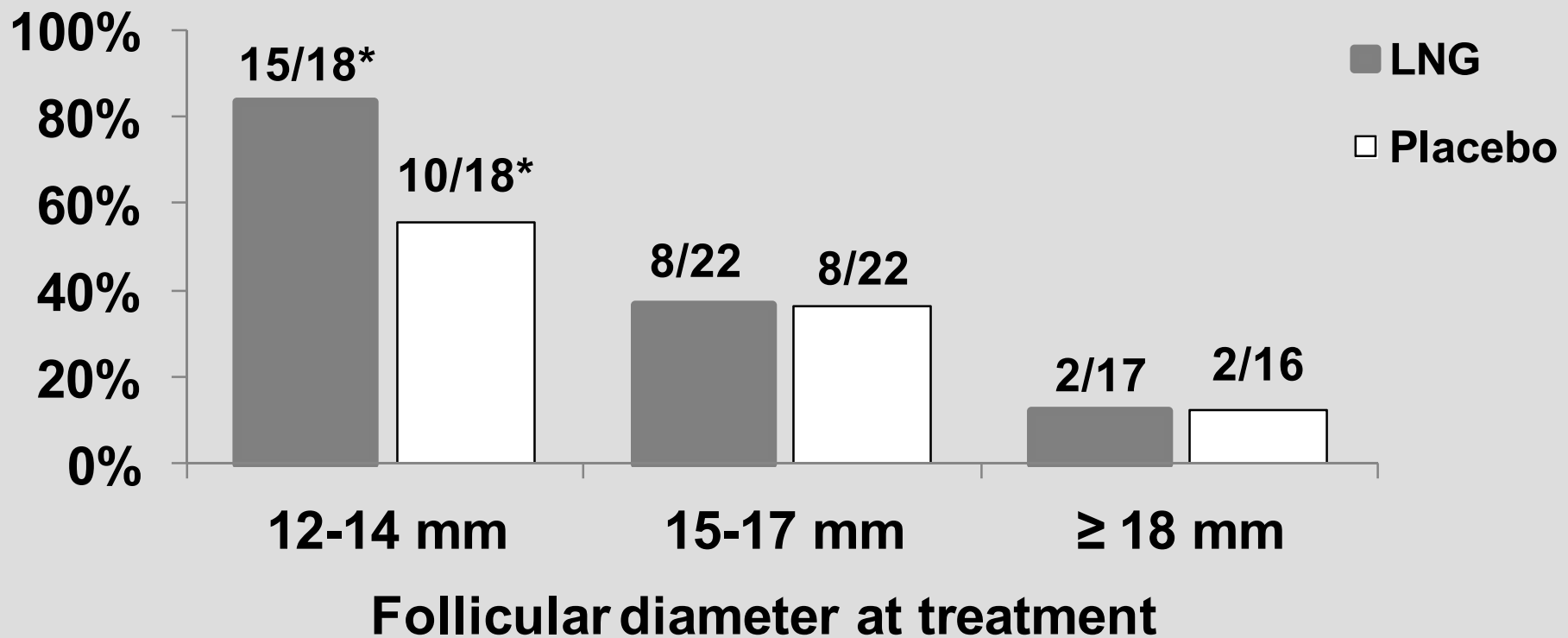
Emergency Contraception Physiological Targets

- ◆ **Inhibiting or attenuating the LH surge**
 - Inhibition or delay of follicular rupture
- ◆ **Altering intrafollicular progesterone action**
 - Inhibition of follicular rupture
 - Possible direct effect on the oocyte, reducing fertilizability

Physiological Target: Follicular Rupture

Levonorgestrel 0.75 mg Twice, 12 Hr Apart

Inhibition of follicular rupture for ≥ 5 days after dosing

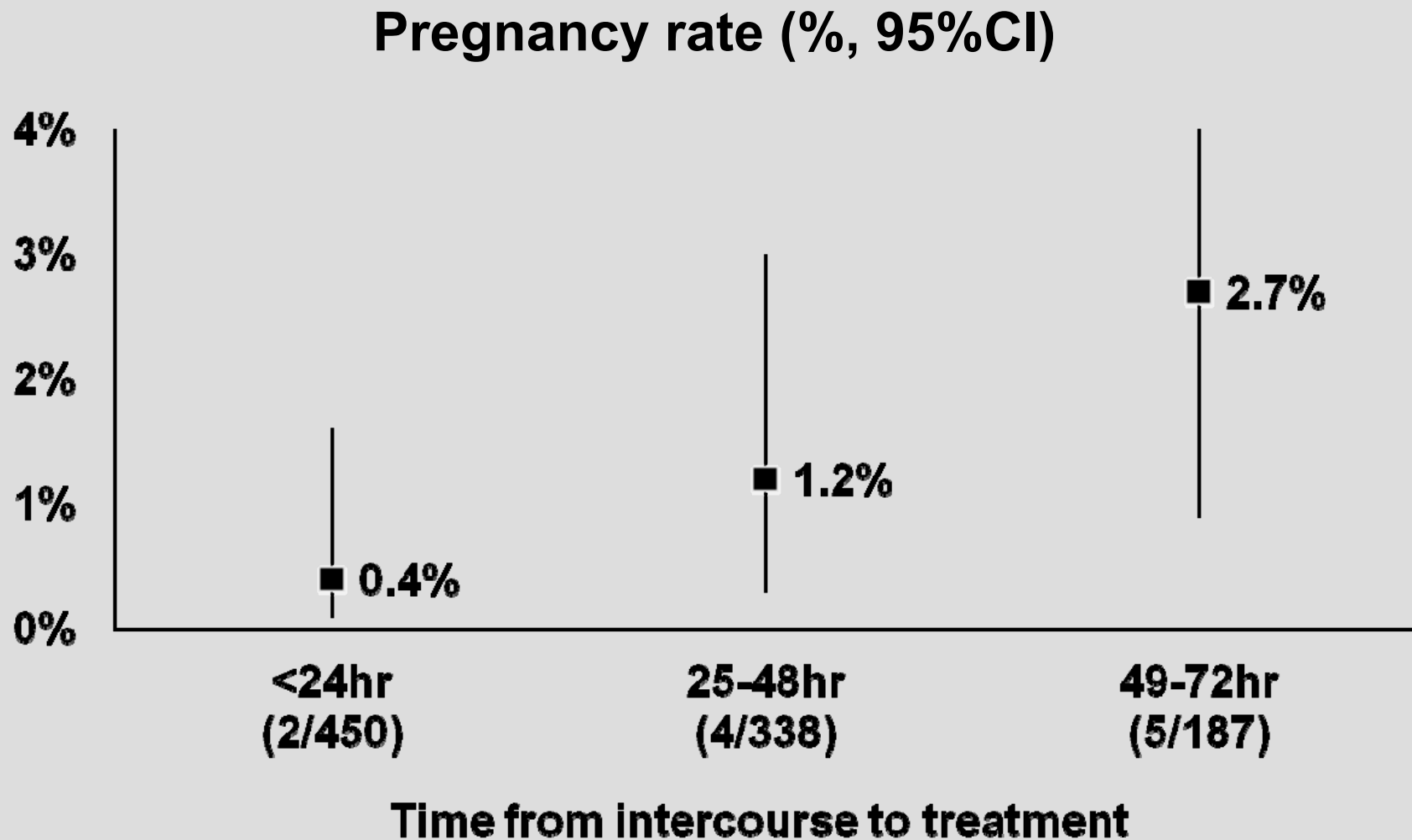


* Statistically significant difference.

Croxatto, et al. *Contraception*. 2004;70:442-450.

Levonorgestrel Efficacy Over Time

0.75 mg Twice, 12 Hr Apart



Unmet Need In Emergency Contraception

- ◆ Existing emergency contraceptives based on levonorgestrel, although widely accessible, have limits
 - Efficacy drops dramatically as time goes by after intercourse
 - Their efficacy is limited by how potently they inhibit ovulation
- ◆ There is a need for a new therapeutic option
 - Consistently inhibits ovulation
 - Consistently efficacious throughout the fertile window
 - Can be used for several days after intercourse

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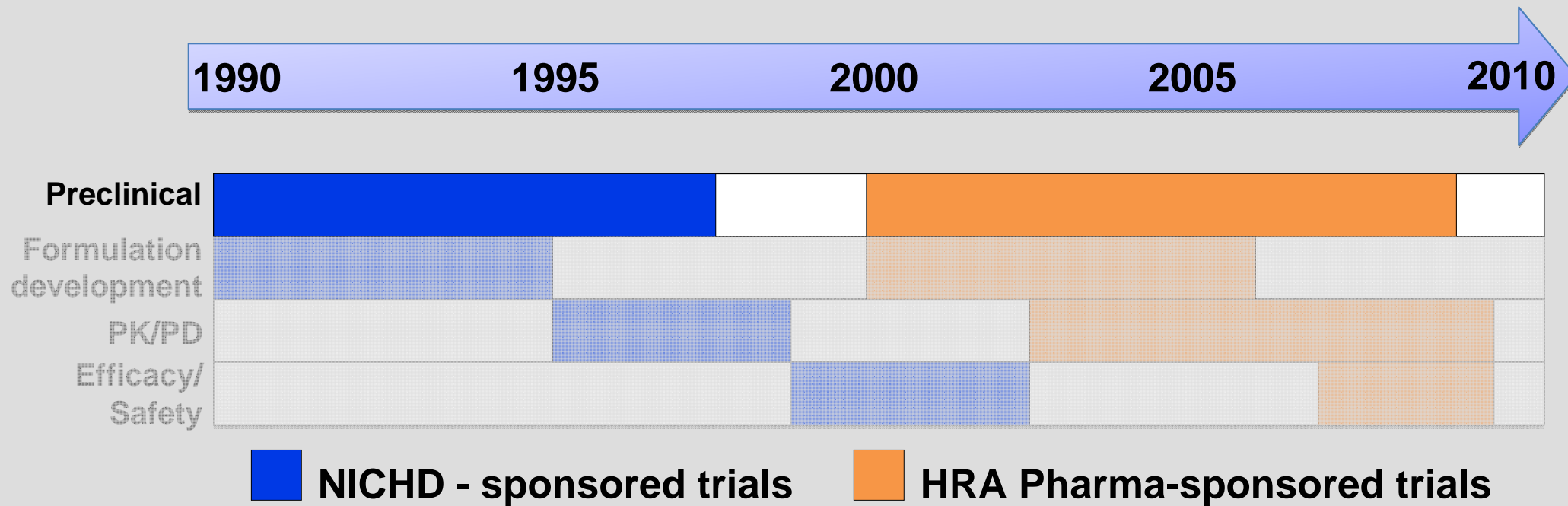
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Development of Ulipristal Acetate



Preclinical Evidence

Primary Pharmacology

◆ Receptor binding

- Strong binding affinity for the progesterone (PR) and glucocorticoid receptors (GR)**
- Much lower affinity for androgen receptor**
- No affinity for estrogen receptor**

◆ Functional activity

- 10-to-30 fold higher potency in antagonizing PR than GR**

Preclinical Evidence

Primary Pharmacology—Study 405

Inhibition of ovulation in rats
(single dose on morning of proestrus)

Dose of UPA (mg/rat)	Ovulating rats/ dosed rats
Control	16/16
0.5	5/8*
1	3/8*
2	0/8*

*p < 0.05 vs control

Reel, et al. *Contraception*. 1998;58:129-136.

Preclinical Evidence

Primary Pharmacology—Study 405

Post-coital contraceptive activity in rats
(dosing days 0-3 post-mating)

Dose of UPA (mg/rat/day)	Pregnant rats/ mated rats
Control	9/10
1	3/10*
2	0/10*
4	0/10*

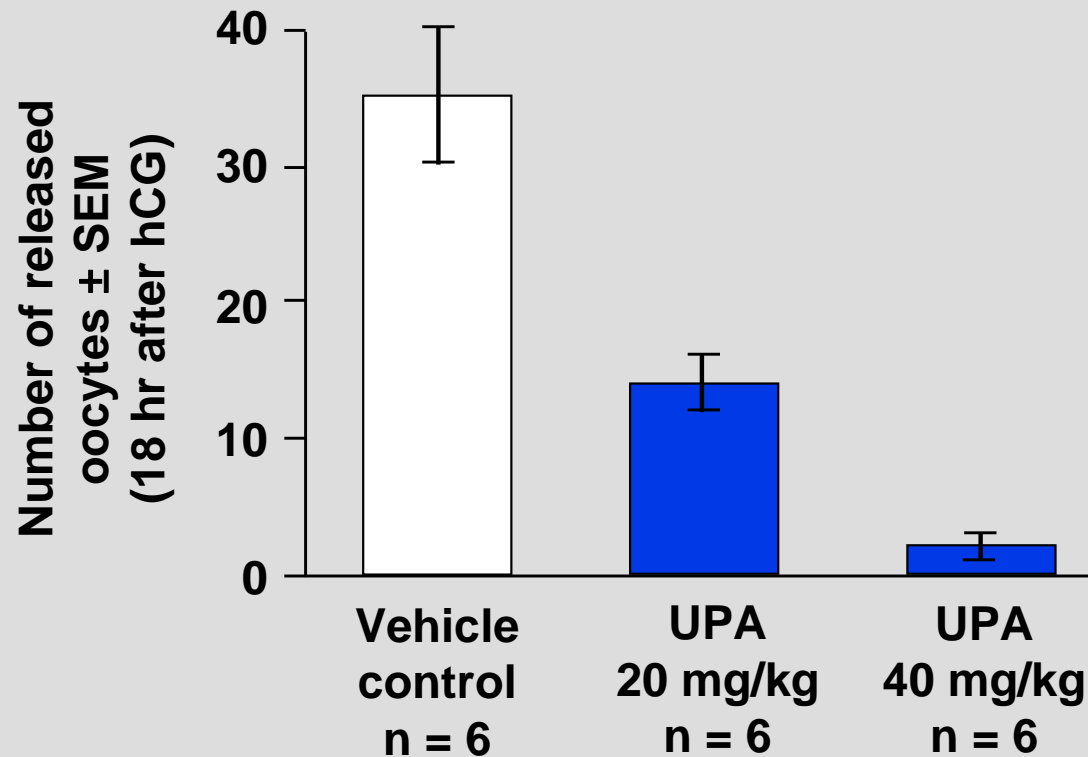
*p < 0.05 vs control

Reel, et al. *Contraception*. 1998;58:129-136.

Preclinical Evidence

Primary Pharmacology

Inhibition of ovulation in gonadotropin-primed mice (*treatment 1 hr before hCG*)



Preclinical Evidence

Repeated-Dose Toxicity—Studies 435, 436

Species	Duration	Dose levels (mg/kg/day)
Rat	14 days	0, 4, 20, 100
	6 months	0, 1, 5, 25
Monkey	14 days	0, 20, 100
	6 months	0, 1, 5, 25

- ◆ No overt systemic toxicity
- ◆ Observations at high doses consistent with action on hypothalamic-pituitary-adrenal and reproductive axes

Preclinical Evidence

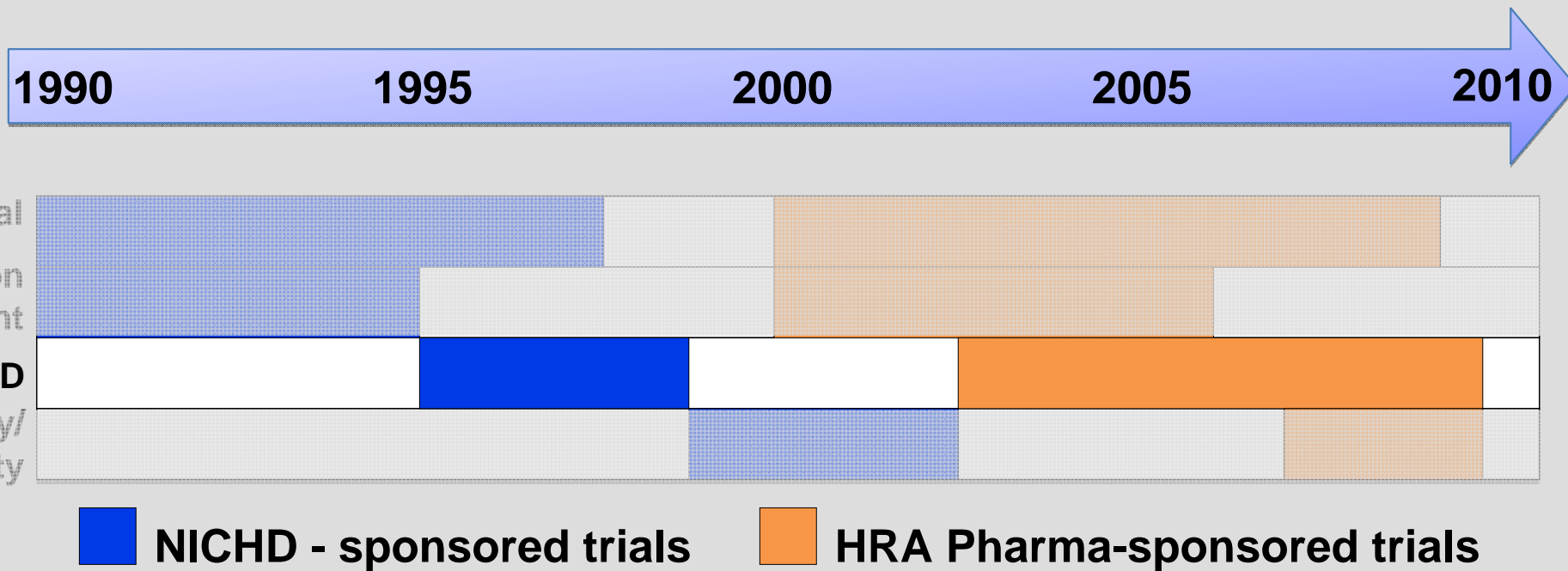
Reproductive Toxicity—Studies 444, 445, 446, 471

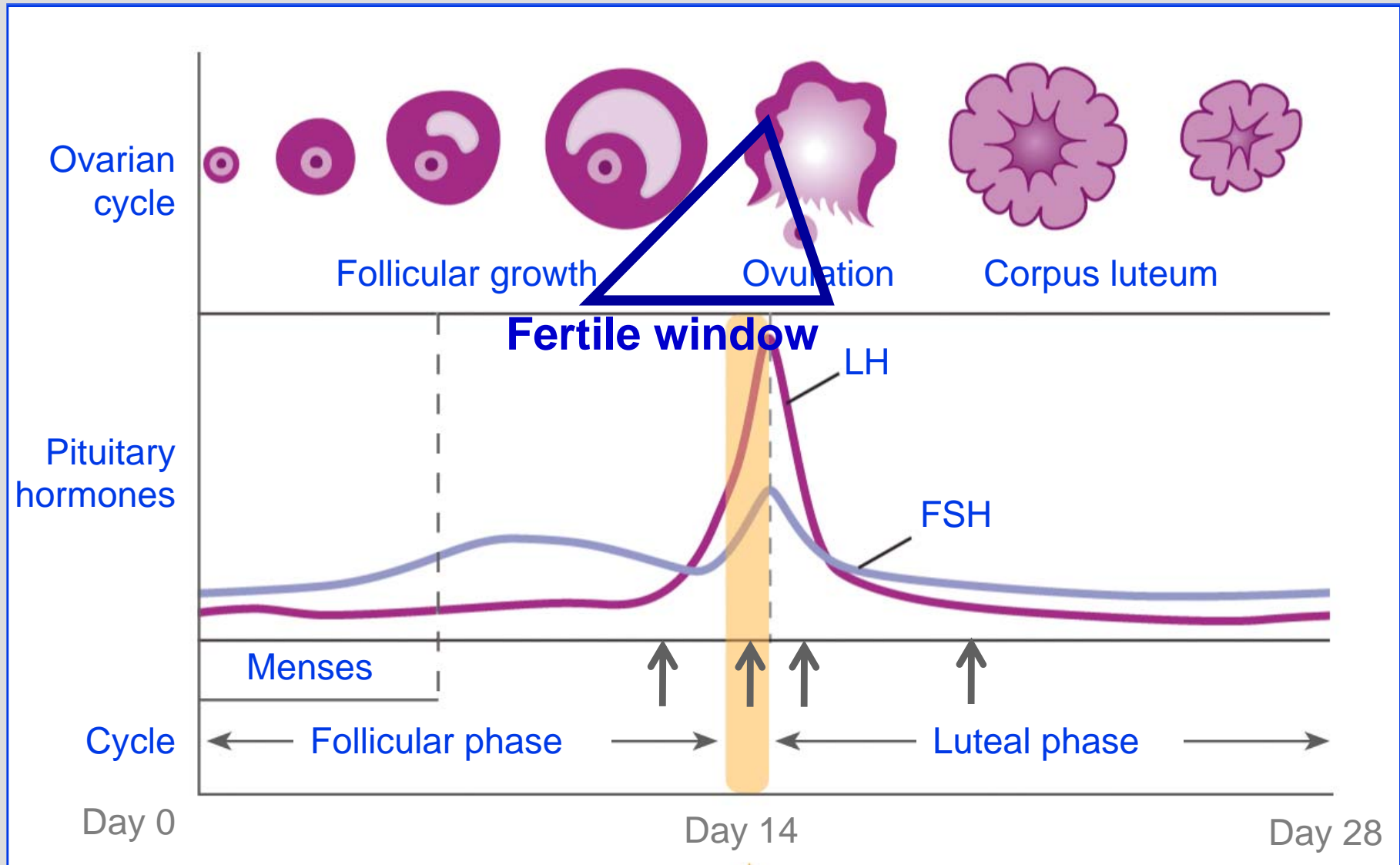
Study	Period of dosing	Dose levels (mg/kg/day)
Rat embryofetal	GD6-GD17	0, 0.1, 0.3, 1.0
Rabbit embryofetal	GD6-GD18	0, 0.1, 0.3, 1.0
Rat pup development	GD0-GD3	0, 0.5, 1.0 mg/rat
Rat peri/post-natal	GD6-LD20	0, 0.03, 0.1, 0.3

GD = gestation day, LD = lactation day

- ◆ Embryofetal studies: no evidence of teratogenicity
- ◆ Pup development and peri/post-natal studies: normal development of F1 generation
- ◆ Limited data at high doses because gestation not consistently maintained

Clinical Development Program Pharmacodynamics





Mid-follicular
(14-16 mm)

Early luteal
(LH+2)

Late follicular
(18 mm)

Mid-luteal
(LH+6/8)

Clinical Development Program

Pharmacodynamic Studies

◆ Might ulipristal acetate be an effective emergency contraceptive?

		Parameters evaluated			
#	Phase	Endocrine function	Follicular development	Endometrial maturation	Menstrual cycle
505	Mid-follicular	✓	✓	✓	✓
511	Late follicular	✓	✓		✓
506	Early luteal	✓		✓	✓
503	Mid-luteal	✓			✓

Clinical Pharmacodynamics

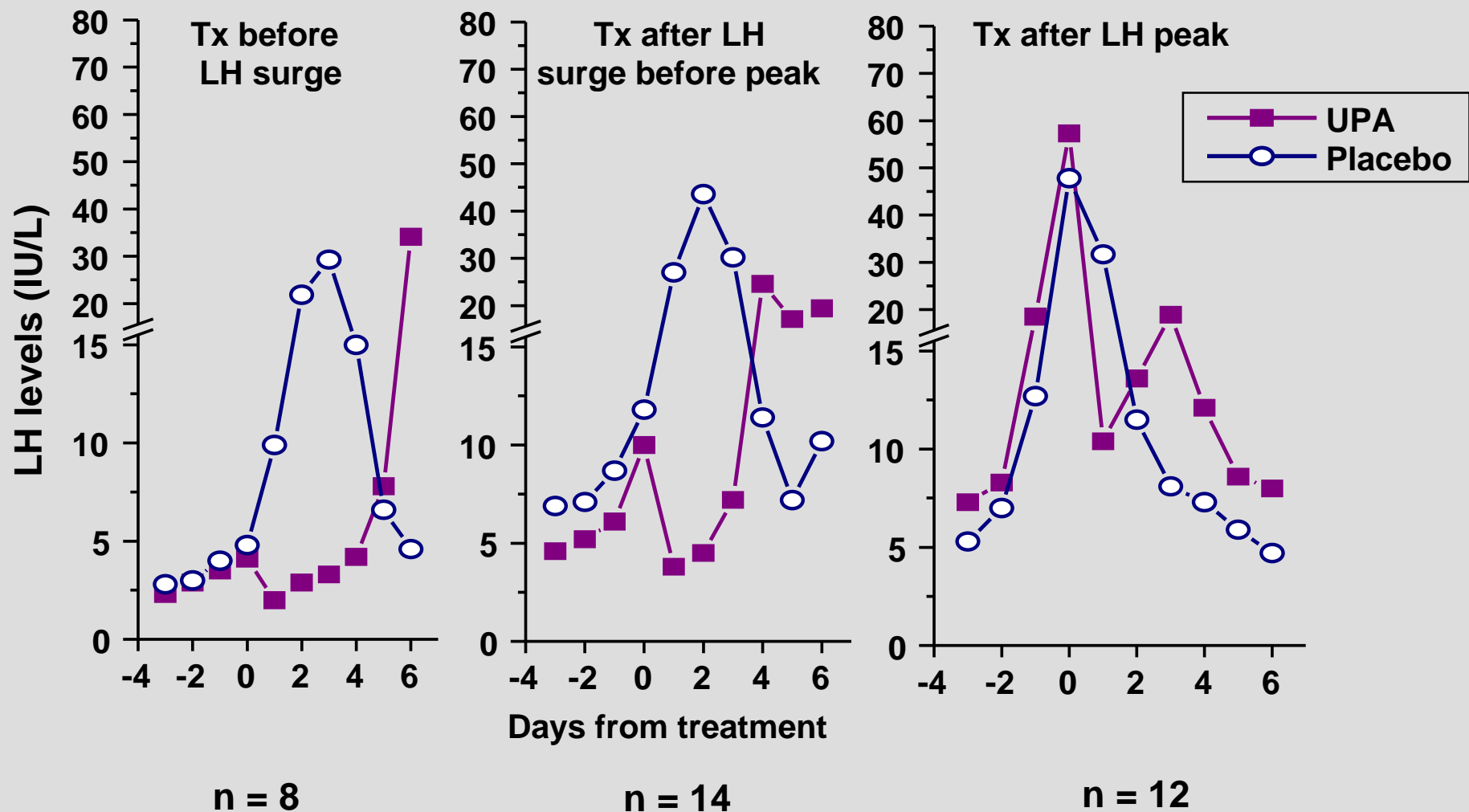
Effects On Endocrine Function

#	Phase	Summary of findings
505	Mid-follicular	Dose-dependent reduction in estradiol for 4 days after dosing Delayed LH surge
511	Late follicular	Drop in estradiol and LH levels immediately after dosing Delayed progesterone rise
506	Early luteal	No effect on mid-luteal estradiol / progesterone concentrations
503	Mid-luteal	No effect on HPA axis or other endocrine function

Effects On Endocrine Function

Study 511—Dose 30 mg

LH levels following late-follicular dosing



Clinical Pharmacodynamics

Effects On Follicular Development

◆ Might ulipristal acetate be an effective emergency contraceptive?

		Parameters evaluated			
#	Phase	Endocrine function	Follicular development	Endometrial maturation	Menstrual cycle
505	Mid-follicular	✓	✓	✓	✓
511	Late follicular	✓	✓		✓
506	Early luteal	✓		✓	✓
503	Mid-luteal	✓			✓

Clinical Pharmacodynamics

Effects On Follicular Development

#	Phase	Summary of findings
505	Mid-follicular	Dose-dependent delay in follicular rupture
511	Late follicular	Delay of follicular rupture in a majority of cycles, even after onset of LH surge

Effects On Follicular Development

Study 505—Dose 10, 50, 100 mg

Time to follicular collapse after mid-follicular dosing

Days from dose to follicular collapse		
Dose	n	Mean (range)
Placebo	12	5.8 (3 - 10)
10 mg	11	6.8 (4 - 16)
50 mg	11	10.3 (7 - 18)
100 mg	10	12.7 (8 - 17)

Clinical Pharmacodynamics

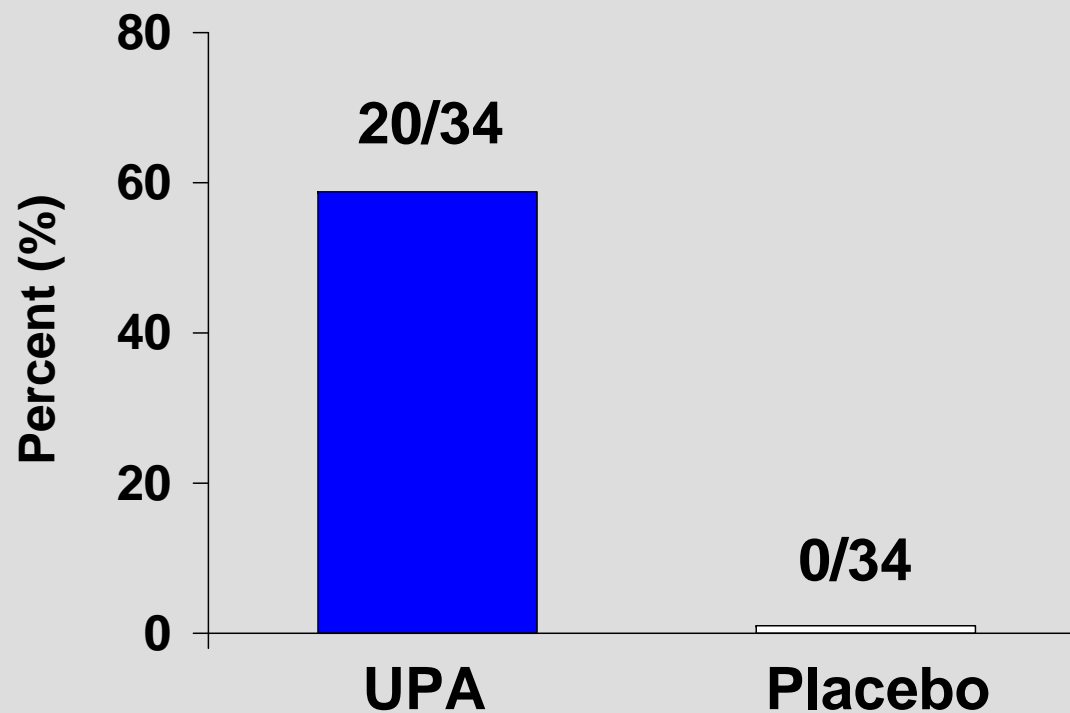
Effects On Follicular Development

#	Phase	Summary of findings
505	Mid-follicular	Dose-dependent delay in follicular rupture
511	Late follicular	Delay of follicular rupture in a majority of cycles, even after onset of LH surge

Effects On Follicular Development

Study 511—Dose 30 mg

Inhibition of follicular rupture for ≥ 5 days after treatment
(late-follicular phase dosing, follicle size ≥ 18 mm)

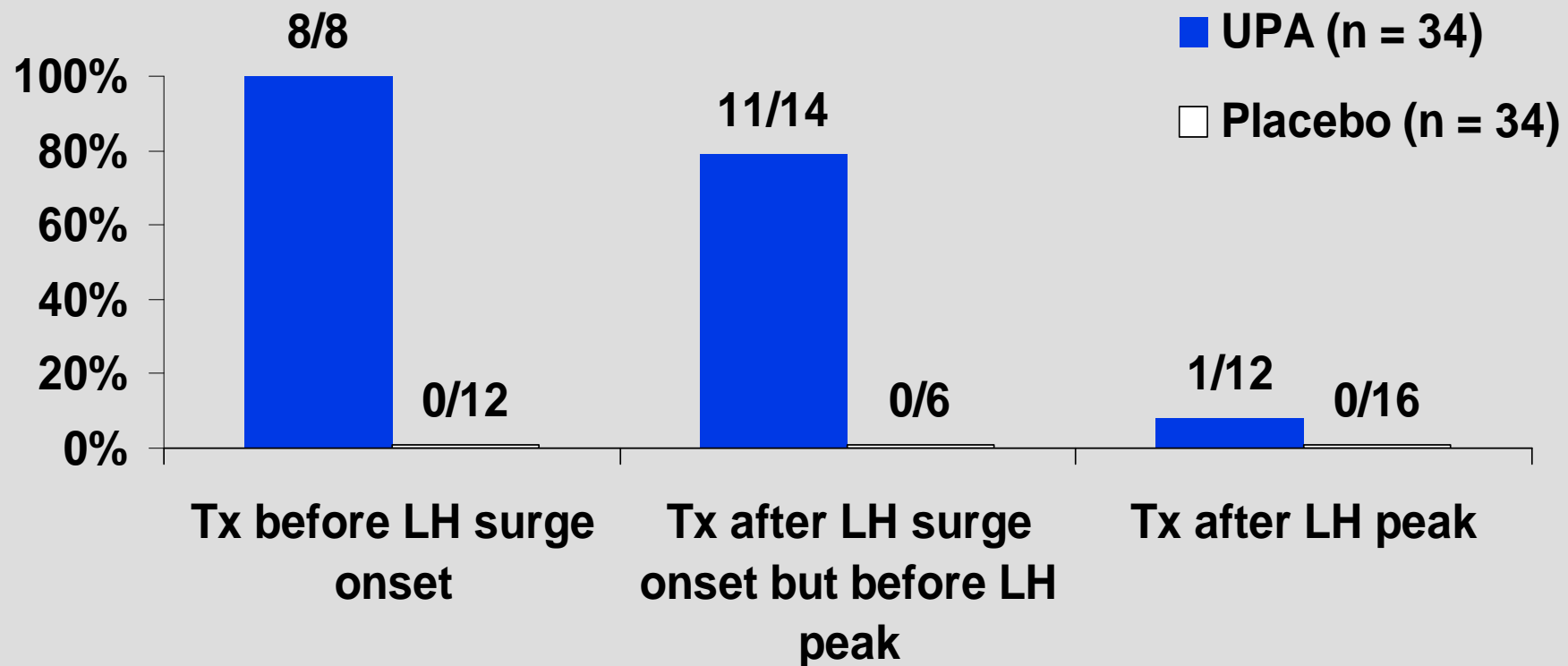


McNemar's test: $p < 0.0001$

Effects On Follicular Development

Study 511—Dose 30 mg

Inhibition of follicular rupture for ≥ 5 days after treatment
(late-follicular phase dosing, follicle size ≥ 18 mm)



Clinical Pharmacodynamics

Effects On Endometrial Maturation

◆ Might ulipristal acetate be an effective emergency contraceptive?

		Parameters evaluated			
#	Phase	Endocrine function	Follicular development	Endometrial maturation	Menstrual cycle
505	Mid-follicular	✓	✓	✓	✓
511	Late follicular	✓	✓		✓
506	Early luteal	✓		✓	✓
503	Mid-luteal	✓			✓

Clinical Pharmacodynamics

Effects On Endometrial Maturation

#	Phase	Summary of findings
505	Mid-follicular	<p>Significant delay of endometrial maturation at all doses</p> <p>No discrepancy between stroma and glandular maturation</p>
506	Early luteal	<p>Non-significant delay in histological endometrial maturation (> 2 days) at highest doses</p> <p>Decreased mean endometrial thickness vs placebo at highest doses</p> <p>Increase in glandular progesterone receptor expression at highest doses</p>

Effects On Endometrial Maturation

Study 505—Dose 10, 50, 100 mg

Mid-follicular effects on luteal phase endometrium

Delayed endometrial
maturation¹

Dose	n	n/total no of women ²
Placebo	12	2/12
10 mg	11	7/11
50 mg	11	7/10
100 mg	10	7/10

1- as determined by Noyes' criteria

2- $p < 0.02$ for trend by Cochran-Armitage

Stratton, et al. *Human Reproduction*. 2000;15(5):1092-1099.

Clinical Pharmacodynamics

Effects On Menstrual Cycle

◆ Might ulipristal acetate be an effective emergency contraceptive?

Parameters evaluated

#	Phase	Endocrine function	Follicular development	Endometrial maturation	Menstrual cycle
505	Mid-follicular	✓	✓	✓	✓
511	Late follicular	✓	✓		✓
506	Early luteal	✓		✓	✓
503	Mid-luteal	✓			✓

Clinical Pharmacodynamics

Effects On Menstrual Cycle

#	Phase	Summary of findings
505	Mid-follicular	No effect on cycle length at 10 mg Increase of 4 days at 50 and 100 mg
511	Late follicular	Average increase of 2.5 days in cycle length No effect on luteal phase length
506	Early luteal	No effect on cycle length or luteal phase length
503	Mid-luteal	No effect on luteal phase length at 1, 10, 50, 100 mg Significant shortening at 200 mg

Effects On Menstrual Cycle

Study 503—Dose 1, 10, 50, 100, 200 mg

Length of luteal phase following mid-luteal phase dosing (LH+6/8)

Dose	n	Length of luteal phase (days)
Placebo	5	13.4 ± 0.5
1 mg	6	13.7 ± 1.0
10 mg	6	13.5 ± 1.1
50 mg	6	11.8 ± 1.2
100 mg	7	13.1 ± 1.2
200 mg	6	9.7 ± 0.3*

*p < 0.02 vs placebo, 1 mg, 10 mg, 100 mg groups.

p = 0.13 vs 50 mg.

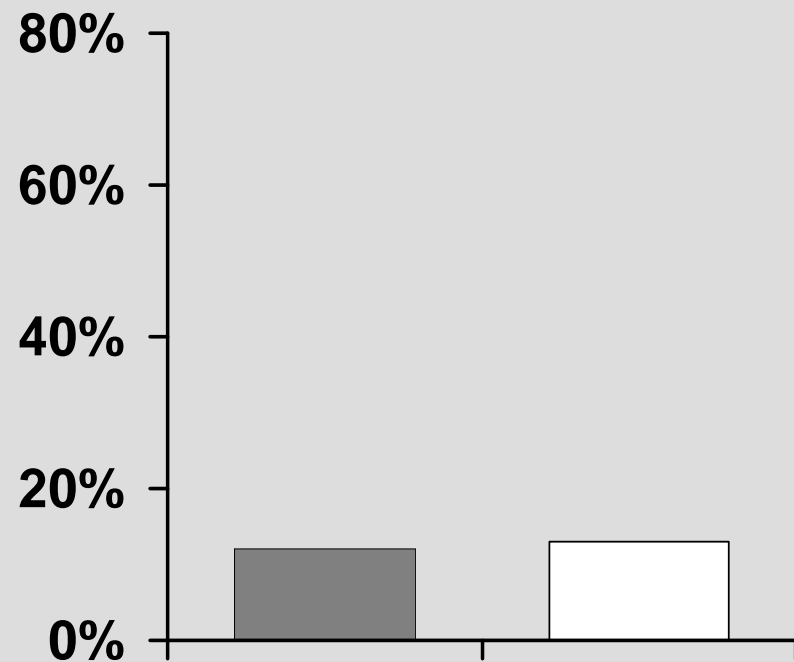
Passaro, et al. *Human Reproduction*. 2003;18 (9):1820-1827.

Pharmacodynamics Summary

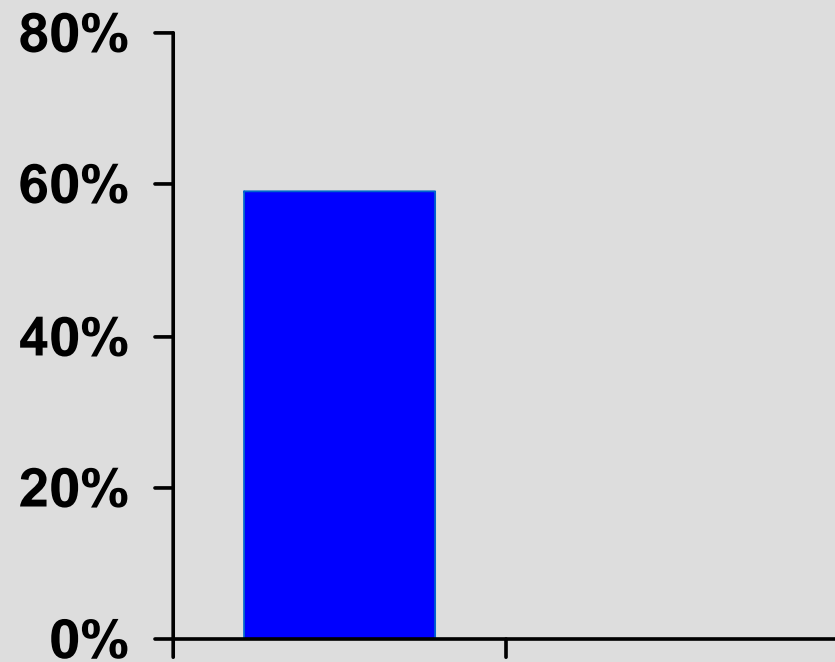
- ◆ **Ulipristal acetate delays ovulation, even after the onset of the LH surge**
- ◆ **Hormonal parameters of the luteal phase and menstrual cycle patterns similar between ulipristal acetate- and placebo-treated women**
- ◆ **Relevance of endometrial modifications unclear**

Presumed Primary Mechanism of Action Inhibition or Delay of Ovulation Study 511—Dose 30 mg

Inhibition of follicular rupture for ≥ 5 days after treatment
(late-follicular phase dosing, follicle size ≥ 18 mm)

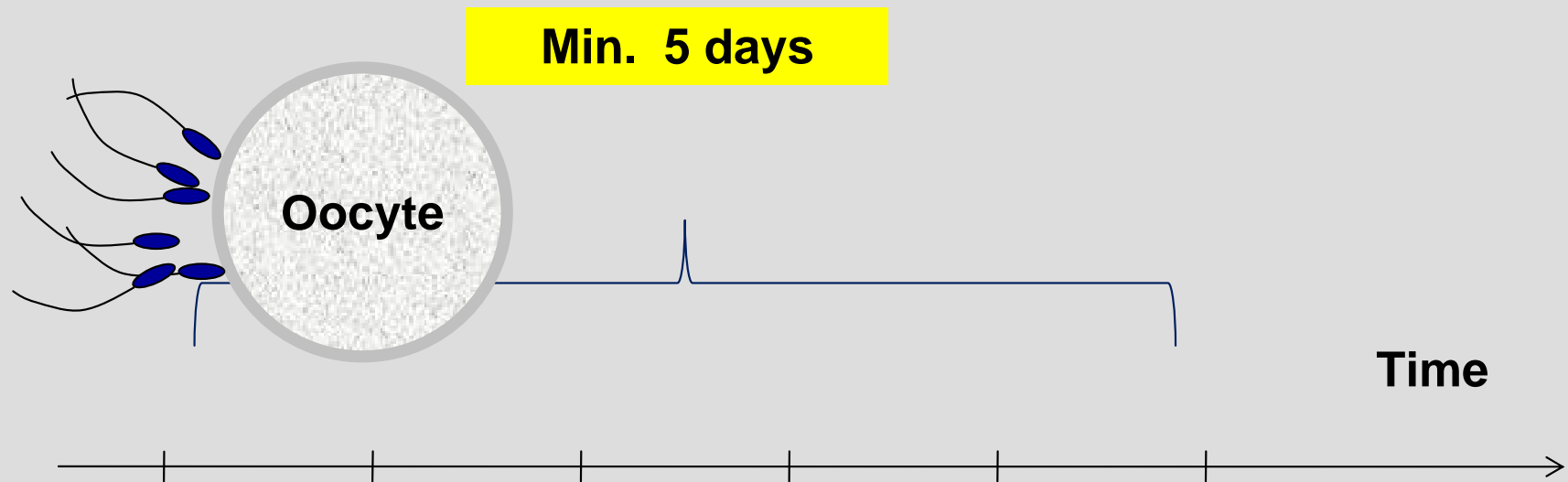


LNG
Placebo
Croxatto, et al.
Contraception. 2004;
70:442-450.



UPA
Placebo
Study 511

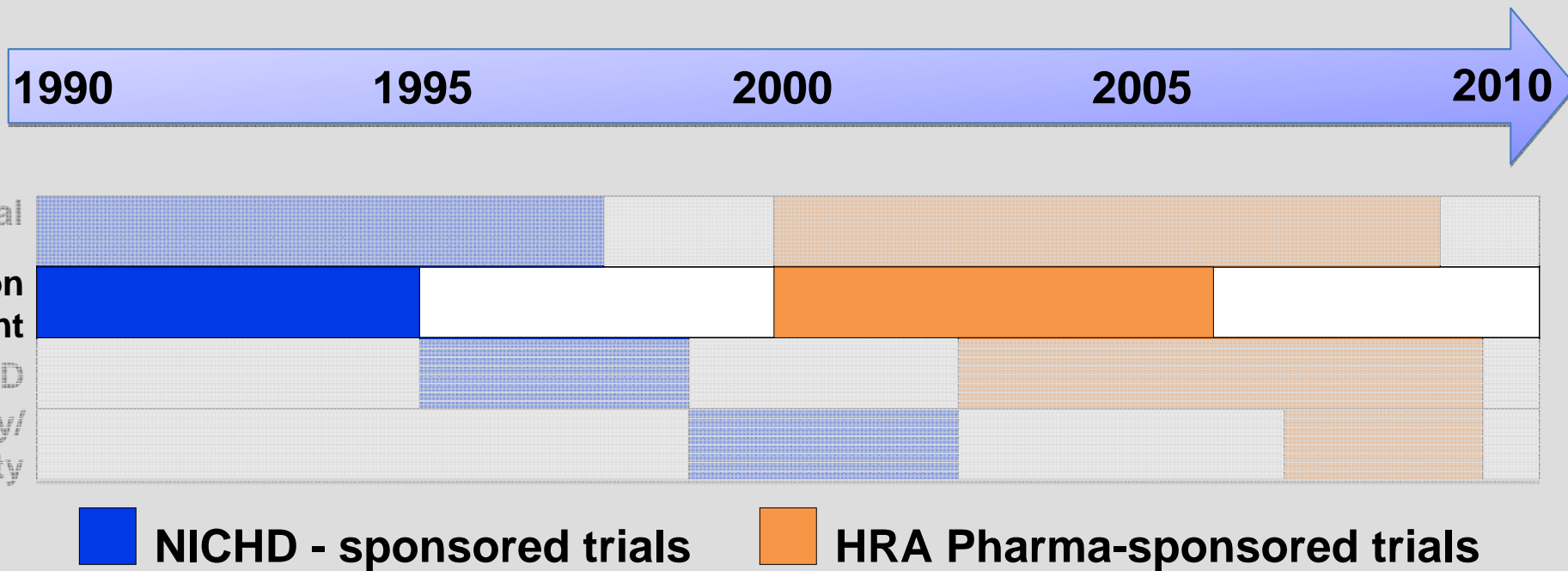
Presumed Primary Mechanism of Action Inhibition or Delay of Ovulation



**Delaying ovulation by ≥ 5 days renders sperm non-viable
and pregnancy is prevented**

Clinical Development Program

Formulation Development



Clinical Development Program

Formulation Development

◆ NICHD formulation

- Gelatin capsule formulations
- Crystalline drug substance



Development of
to-be-marketed
formulation

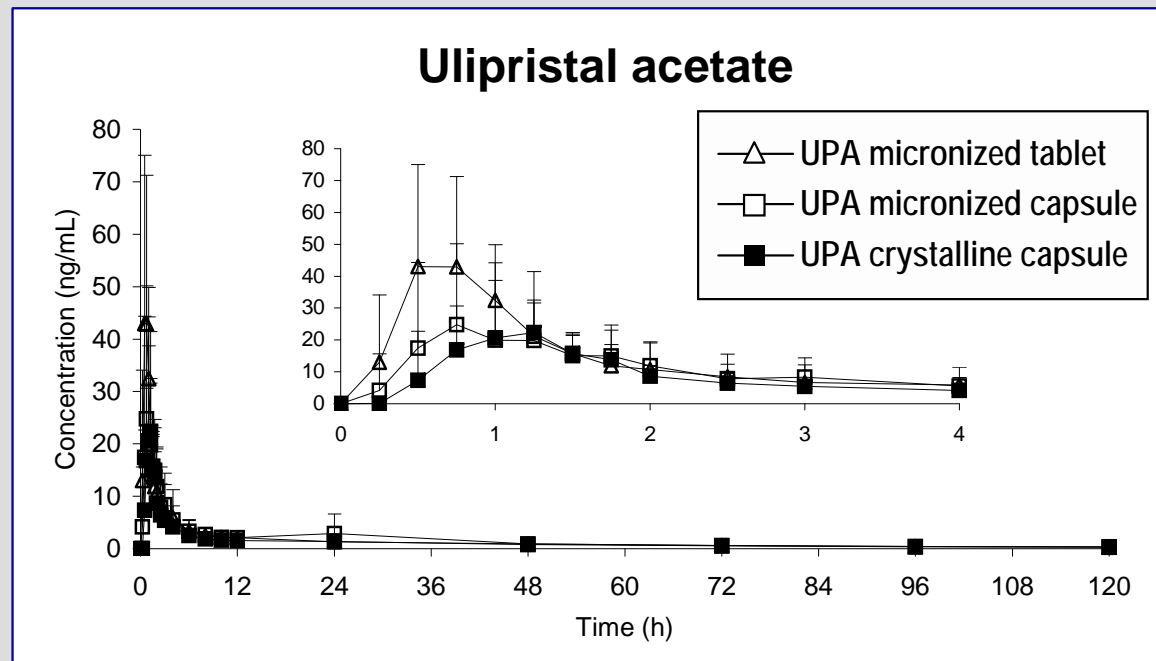
◆ HRA Pharma formulation

- Tablet formulation
- Micronized drug substance

Clinical Development Program

Formulation Development

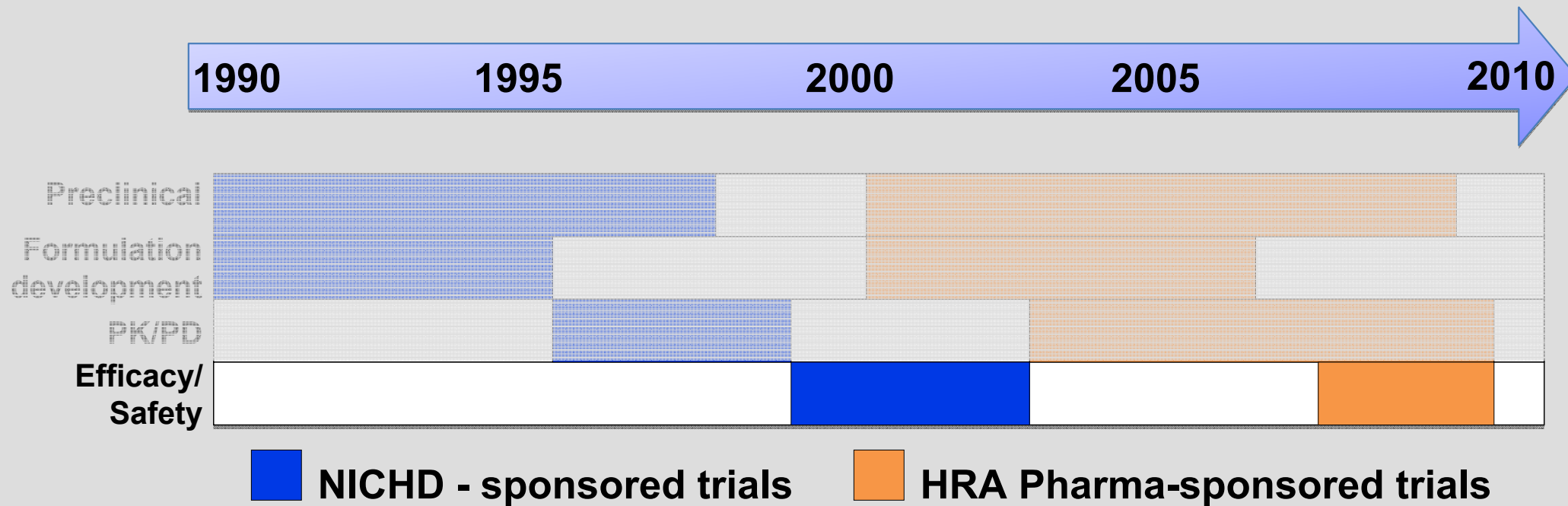
Study 501—Dose 10 mg



- ◆ **Micronized tablet vs crystalline capsule**
 - mean C_{\max} 95% higher
 - mean AUC 40% higher

Efficacy

Clinical Development Program Efficacy



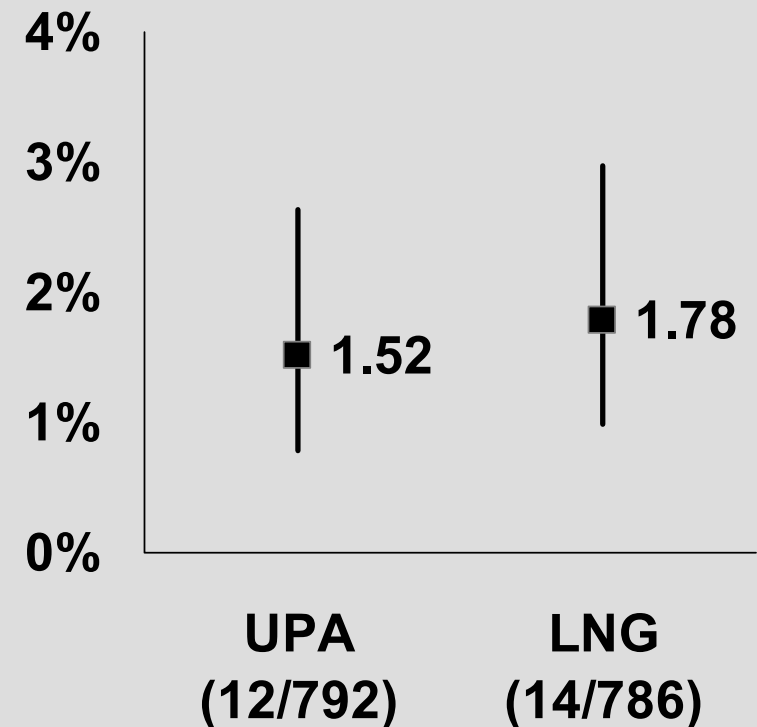
Phase 2/3 Efficacy Trials

Study 507*

Methods

Time window	within 72 hr of intercourse
Study sites	7 clinical sites (USA)
Design	Randomized & double blind
Treatments	UPA 50 mg + placebo 12 hr later LNG 0.75 mg × 2 12 hr apart
Primary efficacy endpoint	Observed pregnancy rate
Hypothesis tested	Non-inferiority UPA to LNG
Sample size for efficacy analysis	770 subjects per group

Observed pregnancy rate
(%, 95% CI)
Primary efficacy
population



* Creinin, et al. *Obstet Gynecol.* 2006;108(5):1089-1097.

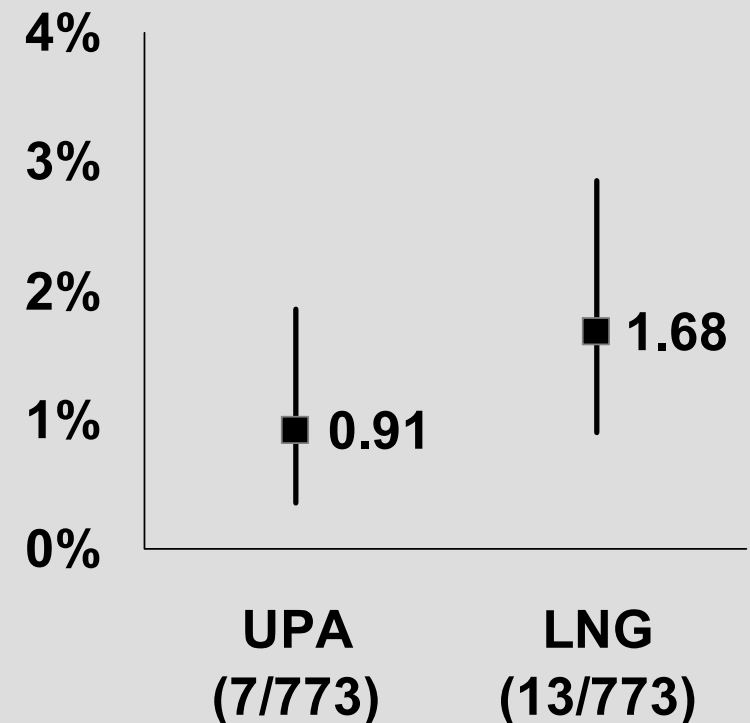
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Treatments	UPA 50 mg + placebo 12 hr later LNG 0.75 mg × 2 12 hr apart
Primary efficacy endpoint	Observed pregnancy rate
Hypothesis tested	Non-inferiority UPA to LNG
Sample size for efficacy analysis	770 subjects per group

Observed pregnancy rate
(%, 95% CI)
Efficacy evaluable
population



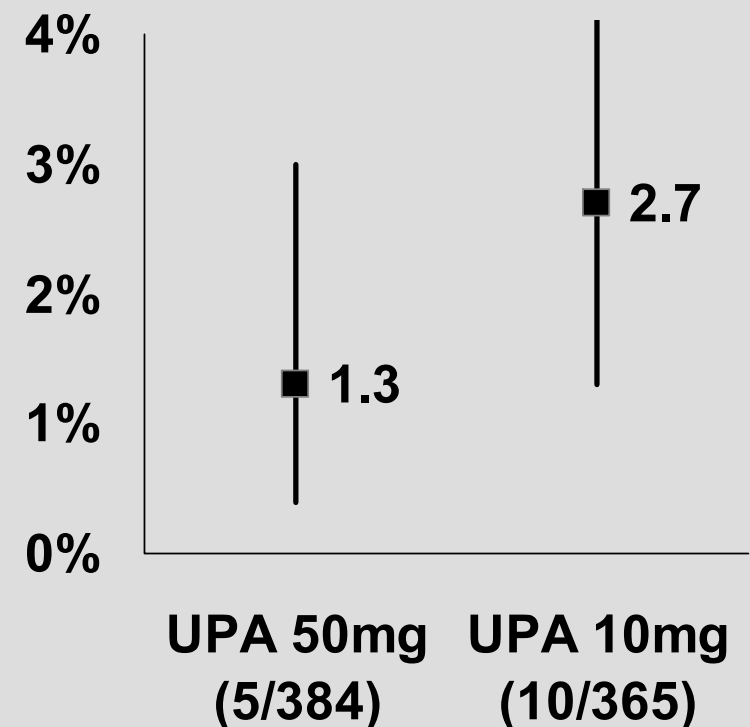
* Creinin, et al. *Obstet Gynecol.* 2006;108(5):1089-1097.

Phase 2/3 Efficacy Trials Study 508

Methods

Time window	within 72 hr of intercourse
Study sites	9 clinical sites (USA)
Design	Randomized & double blind
Treatments	UPA 50 mg UPA 10 mg*
Primary efficacy endpoint	Observed pregnancy rate
Hypothesis tested	Non-inferiority 10 mg to 50 mg
Sample size for efficacy analysis	400 subjects per group

Observed pregnancy rate
(%, 95% CI)
Efficacy evaluable
population



*Initially, a 10-mg unmicronized capsule used. After inclusion of 214 subjects, change was made to a 10-mg micronized capsule due to unacceptably low efficacy of 10 mg unmicronized capsule.

Conclusions

Phase 2/3 Efficacy Trials

- ◆ **Ulipristal acetate is at least as effective as levonorgestrel for emergency contraception within 72 hr of unprotected intercourse or contraceptive failure**
- ◆ **Ulipristal acetate 50 mg appears more effective than micronized ulipristal acetate 10 mg, demonstrating a dose-relationship for efficacy**

Design of pivotal program



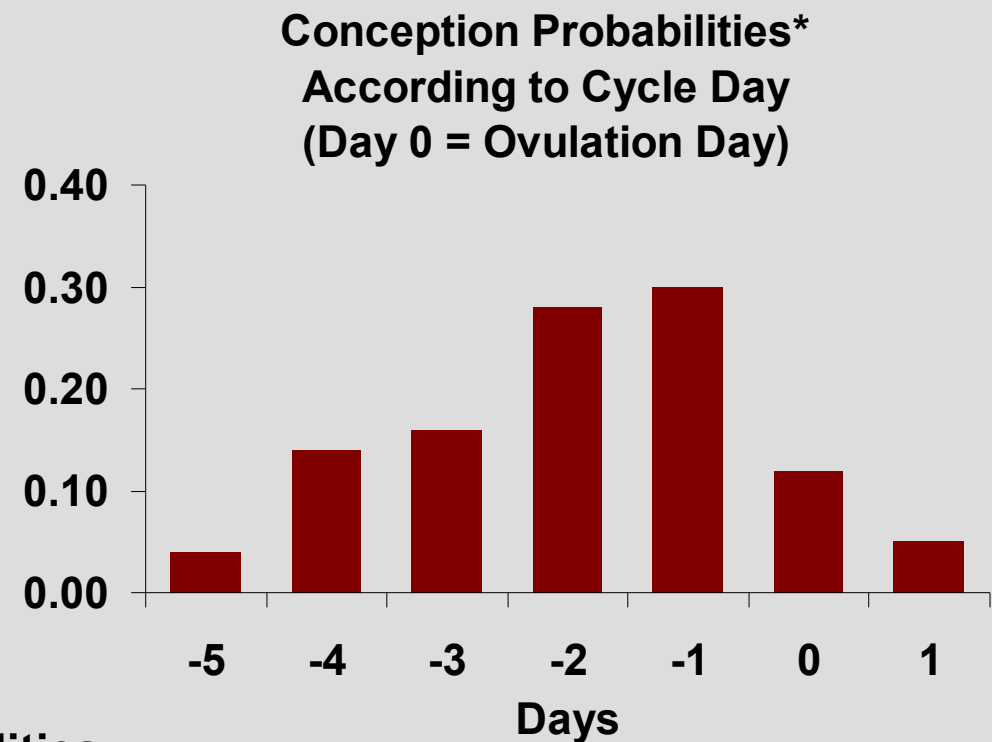
Phase 3 Trials Overview

Study #	509	513
Design	Prospective, Multicenter, Open label	Prospective, Multicenter, Randomized, Single blind
Time window of EC intake	48 - 120 hr	0 - 120 hr (0 - 72 hr for primary efficacy)
Treatment	UPA 30 mg	UPA 30 mg / LNG 1.5 mg
Sample size	1200	910 subjects per group
Interim analysis	@ n = 900	@ n = 1200
Study sites	45 family planning clinics (USA)	35 family planning clinics (24 USA, 10 UK and 1 Ireland)
Primary efficacy analysis	Comparison of the observed pregnancy rate to the expected pregnancy rate	
Primary efficacy population	mITT	
Condition of study success	Positive outcome for primary efficacy analysis AND inferiority to clinical interest limit of 4%	

Primary Efficacy Analysis

Phase 3 Trials

- ◆ Apply conception probabilities per cycle day to study population to calculate expected pregnancy rate
- ◆ Compare expected pregnancy rate to observed pregnancy rate
- ◆ Main secondary analysis (*co-primary*): compare observed pregnancy rate to 4% limit for clinical interest



* Pooled recognizable conception probabilities.
Trussell, et al. *Contraception*. 1998;57:363-366.

Efficacy Analysis Populations

Phase 3 Trials

- ◆ **Primary efficacy population: mITT**
 - Treated, first participation, age ≤ 35 , known pregnancy status
 - Pregnancy compatible with EC failure as assessed by DSMB
- ◆ **Additional efficacy populations**
 - mITT2 population excluded only those pregnancies deemed to have pre-dated treatment
 - ITT completers included all pregnancies

Data Safety Monitoring Board

Phase 3 Trials

- ◆ Reviewed safety data and incidence of pregnancy in each trial
- ◆ Assessed whether each pregnancy was a treatment failure
 - Pre-treatment and follow-up hCG
 - Ultrasound dating
 - Coital history

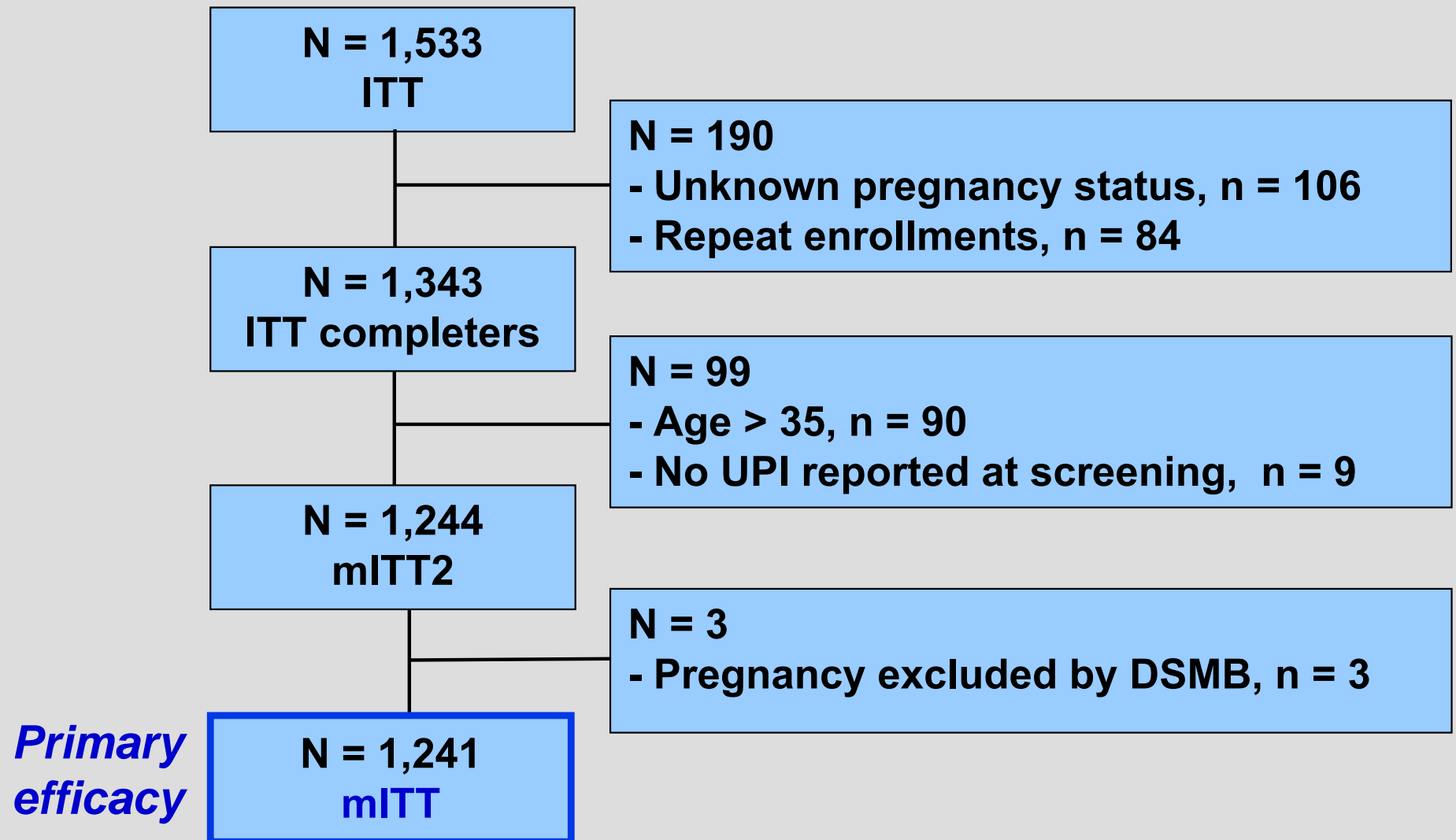
Methods

Phase 3 Trials

Study #	509	513
Design	Prospective, Multicenter, Open label	Prospective, Multicenter, Randomized, Single blind
Time window of EC intake	48 - 120 hr	0 - 120 hr
Treatment	UPA 30 mg	UPA 30 mg / LNG 1.5 mg
Main eligibility criteria	Age 18 and more	Age 16 (UK) / 18 (US) and more
	Regular cycle (24-35 d) / not pregnant Not breastfeeding / no hormonal contraception or IUD	
Study schedule	Women presented requesting emergency contraception Consent, history, pregnancy testing, randomization/ treatment Home diary for AEs, bleeding, coital frequency Follow-up 1 wk after expected menses Systematic high sensitivity pregnancy testing and return of menses Additional visit 1 wk later as needed	

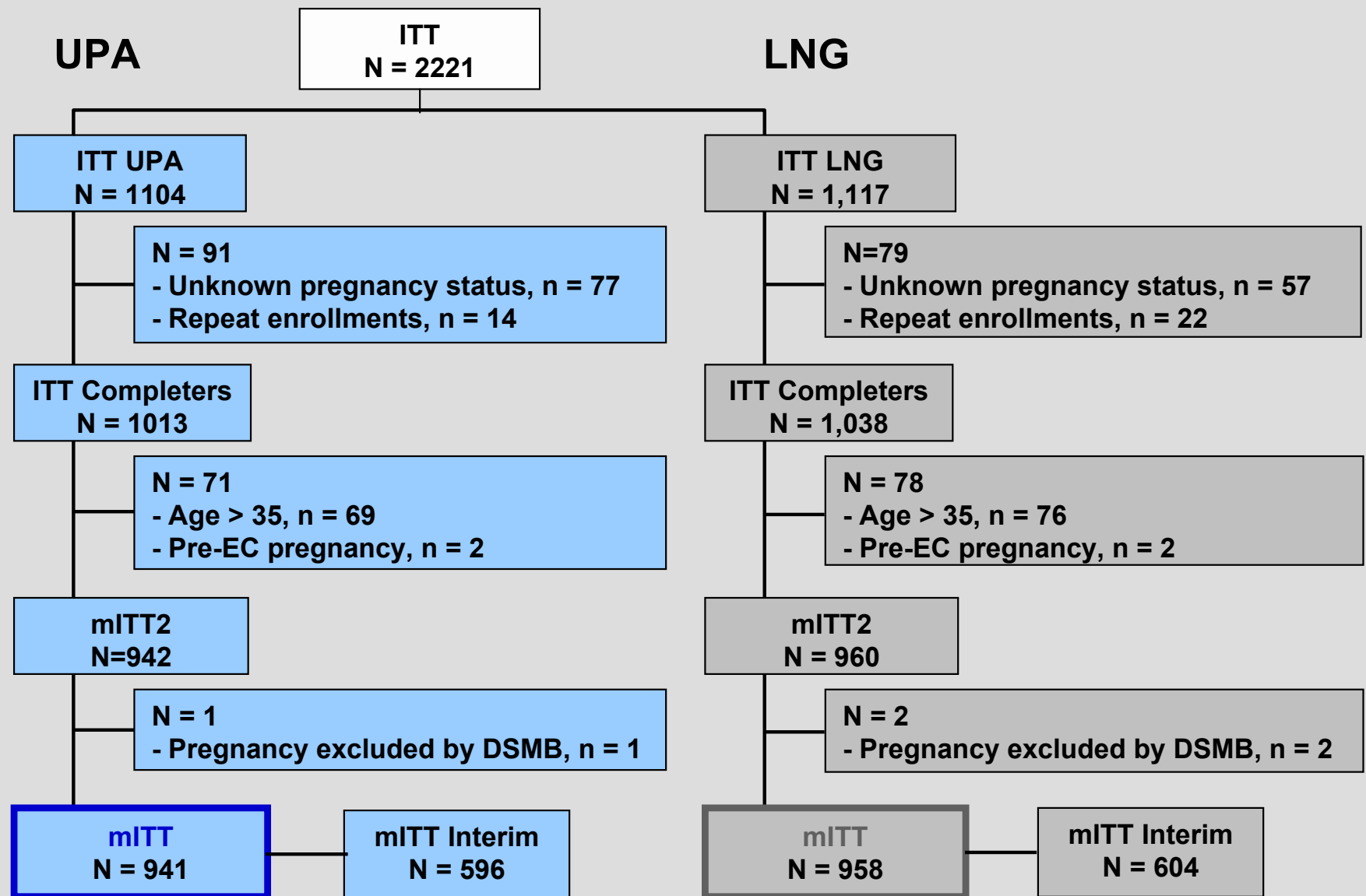
Flow Chart

Study 509—Dose 30 mg



Flow Chart

Study 513—Dose 30 mg



*Primary
efficacy*

Demographics

Phase 3 Trials

Studies 509, 513—Dose 30 mg

Study #		509	513	513
		UPA	UPA	LNG
Characteristics		n = 1533	n = 1104	n = 1117
Age, yrs	Mean \pm SD	24.4 \pm 6.1	24.5 \pm 6.1	24.9 \pm 6.5
	Range, n (%)	18 - 50	16 - 52	16 - 55
Race, n (%)	White	921 (60.3)	804 (72.8)	809 (72.4)
	Black or African American	328 (21.5)	210 (19.0)	207 (18.5)
	Other	279 (18.3)	90 (8.2)	101 (9.1)
BMI (kg/m ²)	Mean \pm SD	25.3 \pm 6.2	25.3 \pm 5.9	25.2 \pm 5.7
Unprotected, n (%)	1	1301 (84.9)	987 (89.4)	988 (88.5)
Intercourse	> 1	223 (14.5)	117 (10.6)	129 (11.5)

Fine, et al. *Obstet Gynecol.* 2010;115:257-263.

Glasier, et al. *Lancet.* 2010;375:555-562.

Time Between Intercourse and Treatment

mITT Phase 3 Study Populations

Studies 509, 513—Dose 30 mg

Study #	Group	Hours				
		0 - 24	>24 - 48	>48 - 72	>72 - 96	>96 - 120
509	UPA			693	390	158
513	UPA	313	338	188	65	35
513	LNG	337	319	196	73	33
Total	UPA	313	338	881	455	193

1,732 (70%)

648 (30%)

Fine, et al. *Obstet Gynecol.* 2010;115:257-263.

Glasier, et al. *Lancet.* 2010;375:555-562.

Primary Efficacy Analysis

Study 509—Dose 30 mg

	48 - 120 hr (mITT) n = 1,241	48 - 120 hr (mITT2) n = 1,244
Observed pregnancies, n	26	29
Observed pregnancy rate, % (95% CI)	2.10 (1.41 - 3.10)	2.33 (1.60 - 3.37)
Expected pregnancy rate, %	5.53	5.54

**Results met protocol definition of study success;
observed pregnancy rate lower than expected
pregnancy rate and lower than 4%**

Primary Efficacy Analysis

Study 513—Dose 30 mg

	0 - 72 hr mITT Interim n = 596	0 - 72 hr mITT n = 843	0 - 72 hr mITT2 n = 844	0 - 120 hr mITT n = 939
Observed pregnancies, n	9	15	16	15
Observed pregnancy rate, % (95% CI)	1.51 (0.62 - 3.32)	1.78 (1.04 - 2.98)	1.90 (1.13 - 3.12)	1.60 (0.93 - 2.67)
Expected pregnancy rate, %	5.63	5.54	5.55	5.72

**Results met protocol definition of study success;
observed pregnancy rate lower than expected
pregnancy rate and lower than 4%**

Additional Efficacy Analyses

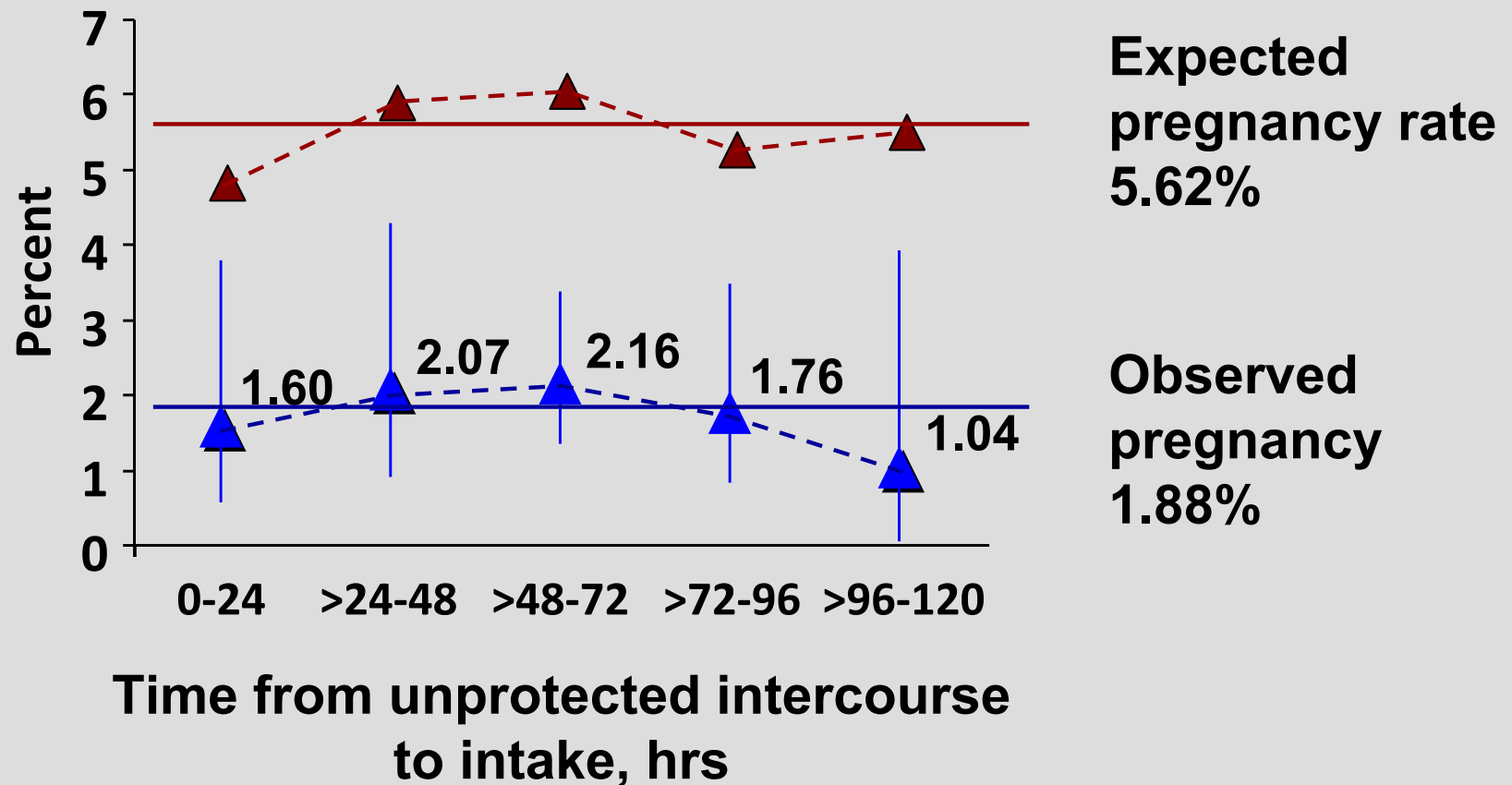
- ◆ **Trend in pregnancy rates over time**
 - Phase 3 studies (509 & 513), individually and pooled
- ◆ **Efficacy vs levonorgestrel**
 - Active-controlled studies (507 & 513), individually and pooled
- ◆ **Subgroup analyses**
 - Pooled phase 3 database
 - Meta-analysis of active-controlled studies (507 & 513)

Trend in Pregnancy Rates Over Time

mITT Pooled Phase 3 Population

Studies 509, 513—Dose 30 mg

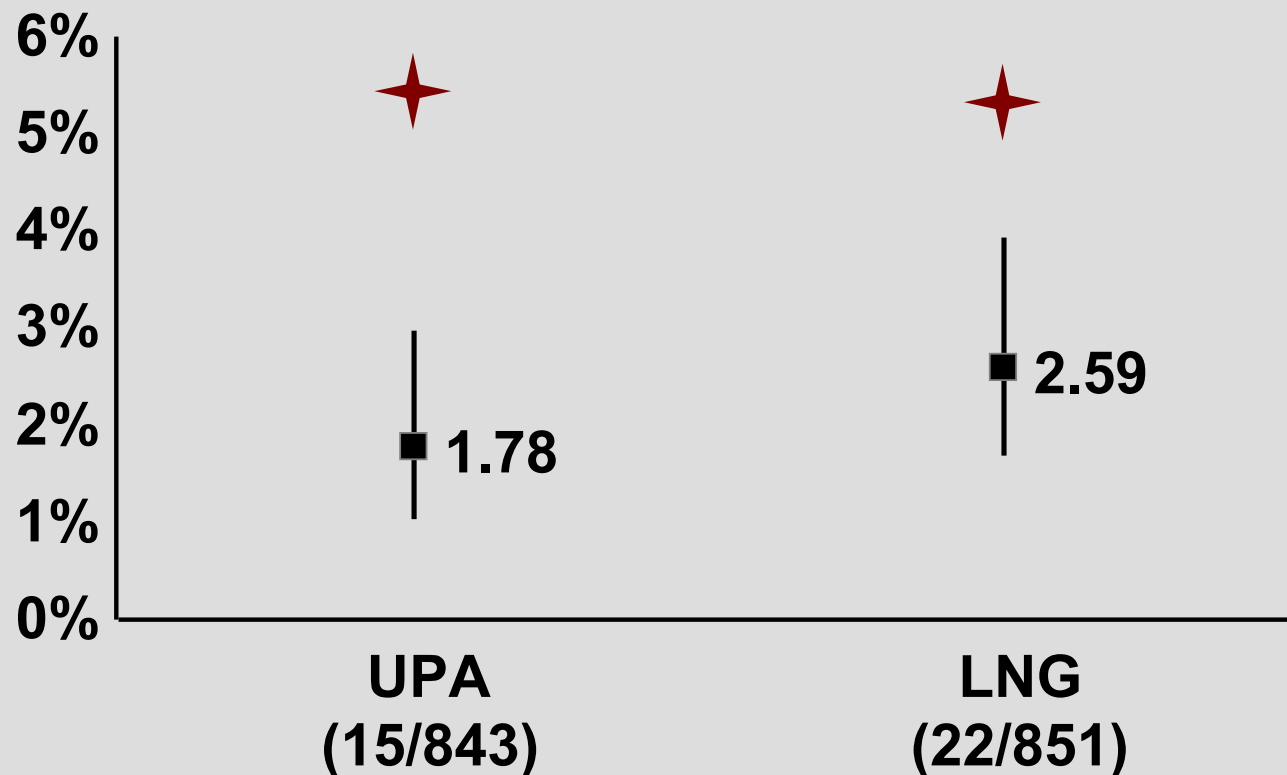
Expected and observed pregnancy rates per 24-hr interval



Efficacy vs Levonorgestrel

Study 513 mITT Population (0-72 hr)—Dose 30 mg

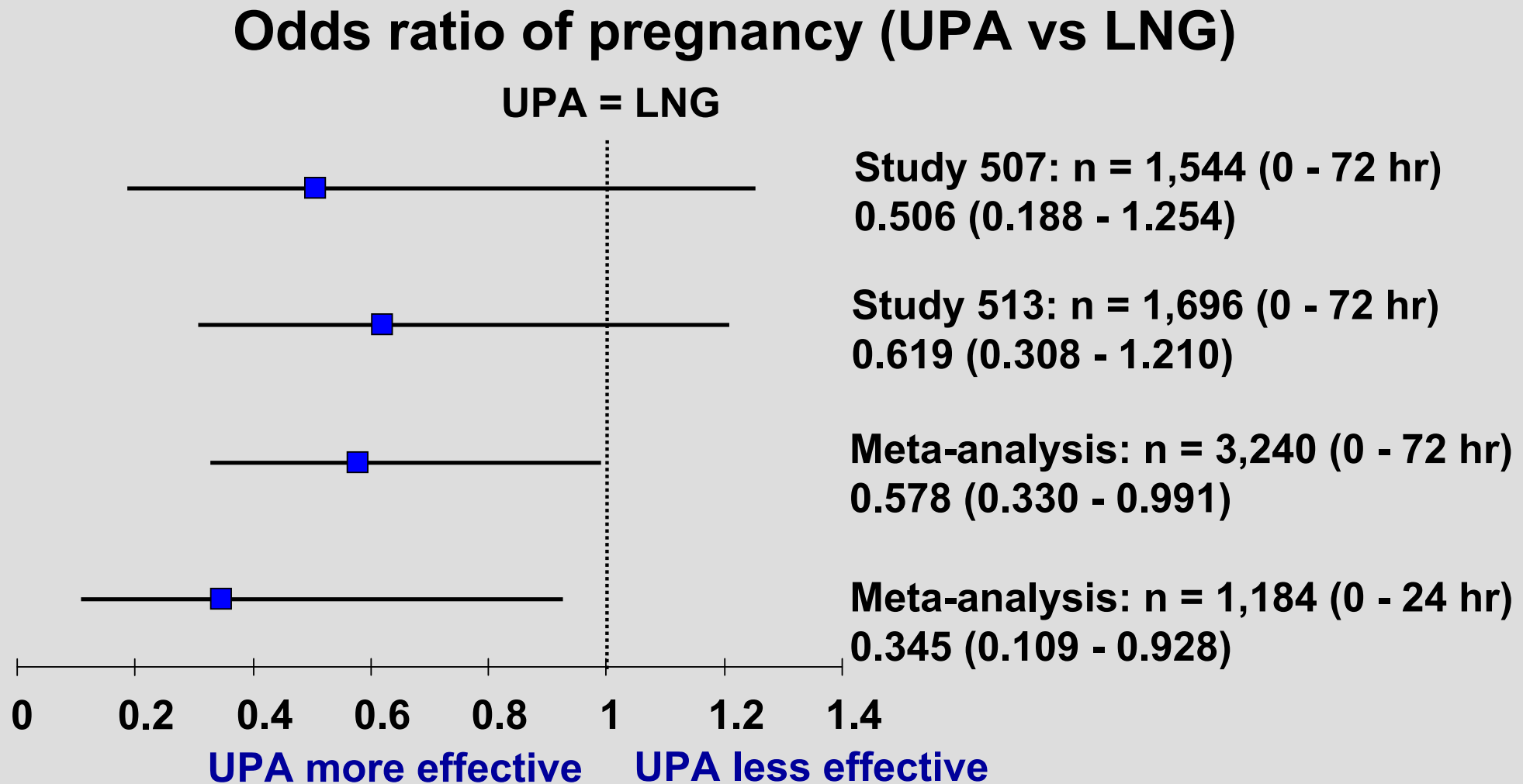
Observed and expected (✦) pregnancy rate (% , 95%CI)



Efficacy vs Levonorgestrel

Pooled Active-Controlled Studies

Studies 507, 513—Dose 30 mg, 50 mg



Subgroup Analyses

Pooled Phase 3 Study Populations

Studies 509, 513—Dose 30 mg

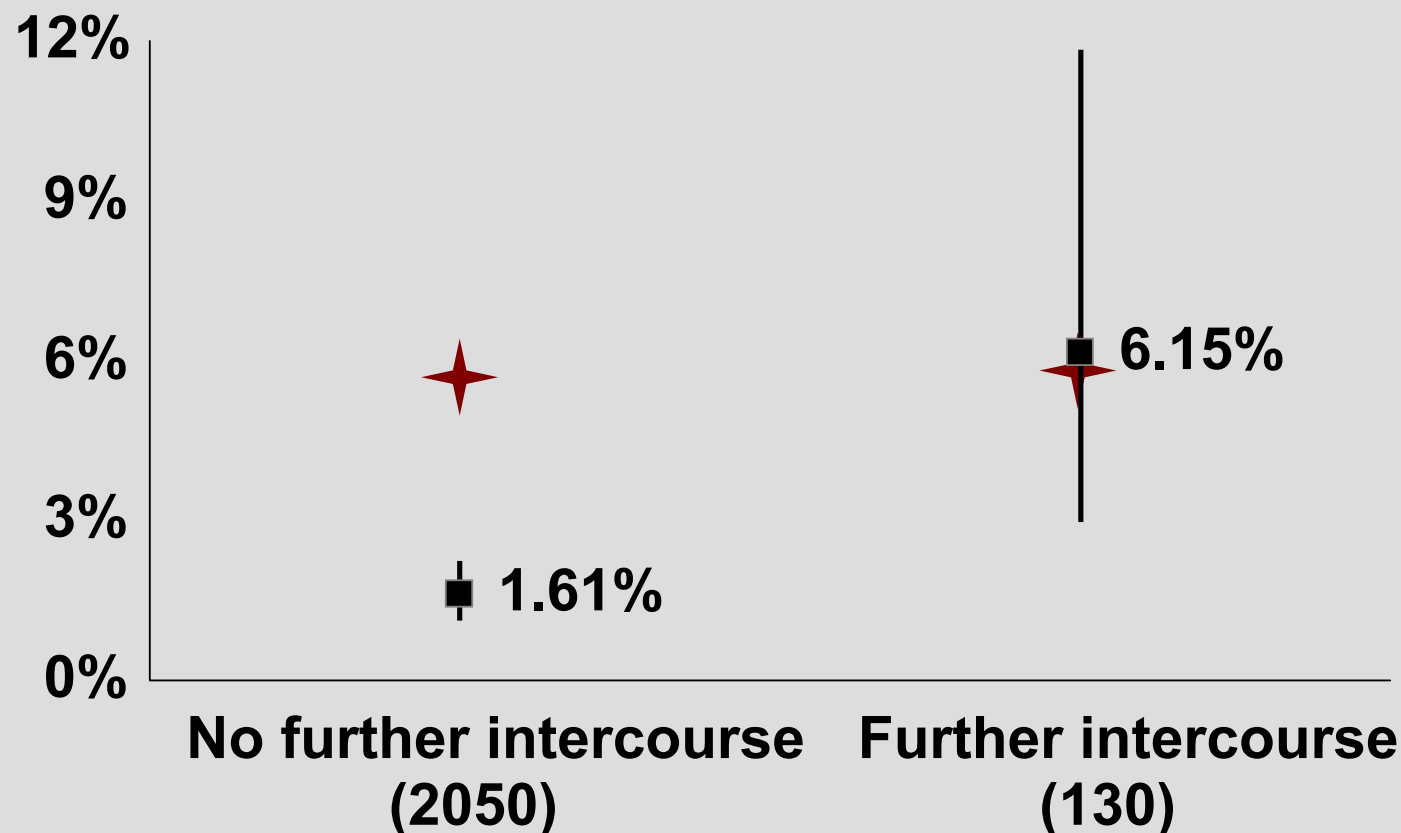
- ◆ **Pregnancy rates consistent across categories of**
 - Age
 - Race
 - Region (US vs Europe)
 - Food intake
 - History of pregnancy
 - Repeat use of ulipristal acetate
 - Concomitant diseases or medications
- ◆ **Factors that account for treatment failure**
 - Further intercourse
 - Body mass index (BMI)

Subgroup Analysis: Further Intercourse

Pooled Phase 3 mITT Population

Studies 509, 513—Dose 30 mg

Observed and expected (★) pregnancy rate (% , 95%CI)



Subgroup Analysis: BMI

Pooled Phase 3 mITT Population

Studies 509, 513—Dose 30 mg

BMI range (kg/m ²)	n	Observed pregnancy rate, % (95%CI)		Expected pregnancy rate, %
< 25	1322	1.66	(1.09 - 2.52)	5.72
25 - 27	253	0.79	(0.03 - 3.03)	5.61
> 27 - 30	252	2.38	(0.97 - 5.22)	6.68
> 30	351	3.13	(1.69 - 5.59)	4.55

Subgroup Analysis: BMI

Pooled Active-Controlled Studies

Studies 507, 513—Dose 30 mg, 50 mg

BMI range (kg/m ²)	WHO class	N	Pregnancy rate, % (95%CI)	
			Ulipristal acetate	Levonorgestrel
< 18.5	Underweight	145	0 (0 - 7.07)	1.4 (0.03 - 7.43)
18.5 - 24.9	Normal wt	2087	1.2 (0.60 - 2.03)	1.3 (0.72 - 2.24)
25 - 29.9	Overweight	744	1.1 (0.29 - 2.72)	2.5 (1.12 - 4.65)
30 - 34.9	Obese grade I	285	1.5 (0.18 - 5.31)	6.7 (3.22 - 12.35)
35 - 39.9	Obese grade II	107	3.6 (0.44 - 13.13)	3.9 (0.46 - 13.88)
≥ 40	Obese grade III	77	5.6 (0.66 - 20.05)	4.9 (0.59 - 17.61)

Efficacy Summary

- ◆ **Broad representative study population**
- ◆ **Both Phase 3 studies met SPA predefined primary efficacy endpoints**
- ◆ **Ulipristal acetate consistently reduced pregnancy risk across all efficacy trials**
- ◆ **Ulipristal acetate consistently effective up to 120 hr after intercourse**
- ◆ **All secondary and sensitivity analyses supported the primary efficacy results**

Agenda

Introduction

Erin Gainer, PhD, MPH
CEO, HRA Pharma

History of Emergency Contraception

James Trussell, PhD
*Prof. of Economics and Public Affairs
Director, Office of Population Research,
Princeton University*

Mechanism of Action of Emergency
Contraception

David Archer, MD
*Prof. of Obstetrics & Gynecology
Director Clinical Research Center Eastern
Virginia Medical School*

Pharmacodynamics and Efficacy of
Ulipristal Acetate

Erin Gainer, PhD, MPH

Safety of Ulipristal Acetate

Delphine Lévy, MD
Head of Medical Affairs, HRA Pharma

Benefit/Risk and Conclusions

Erin Gainer, PhD, MPH

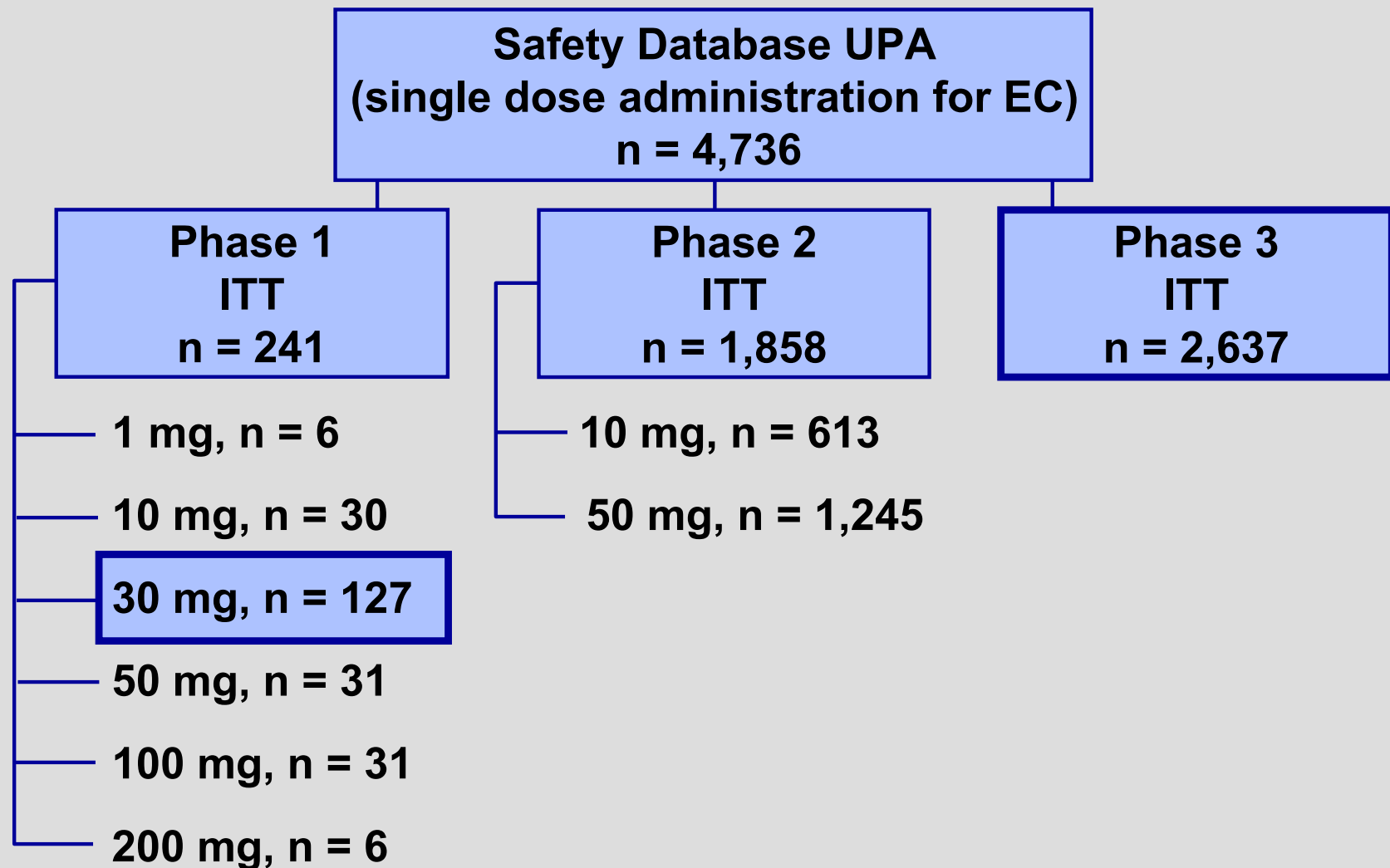
Safety of Ulipristal Acetate

Delphine Lévy, MD

Head of Medical Affairs, HRA Pharma

Overall Clinical Safety Database

Single Dose Administration



Overall Clinical Safety Database

Repeated Dose Administration

Phase 1

Study	Treatment dose	N	Treatment duration
510 (PD)	2.5 mg	12	84 days
	5 mg	12	
	10 mg	11	

Phase 3

Study	Treatment dose	N	N of intakes
509 & 513	30 mg	84	75 twice
			9 three times

Collection of Safety Data

AEs	Collected systematically from consent to end of study
Menstrual cycle length and bleeding patterns	Evaluated in all PD, Phase 2 & 3 studies
Systematic transvaginal U/S	To document follicular development: in 3 PD studies
Clinical chemistry/hematology	In all PK and PD studies and a subset of subjects in Phase 3 study 509
Vital signs	In all PK-PD studies
Hormone assays	E2/P4/FSH/LH in all PD studies; and prolactin, renin, ACTH, cortisol and TSH/thyroxine in certain studies
Endometrial histology	Biopsies performed in 2 Phase 1 dose-ranging studies with single dose and in 84-day daily dosing study

Serious Adverse Events

Single Dose Administration

Study # n dose	Phase 1		Phase 2	Phase 3	
	504 20 30 mg	512 19 30 mg	507 832 50 mg	509 1,533 30 mg	513 1,104 30 mg
Bacterial pneumopathy	1				
Corneal ulcer					1
Dizziness					1*
Kidney infection			1		
Optic nerve hypoplasia				1	
Pelvic inflammatory disease			1		
Pilonidal cyst		1			
Seizure				1	
Urinary tract infection					1

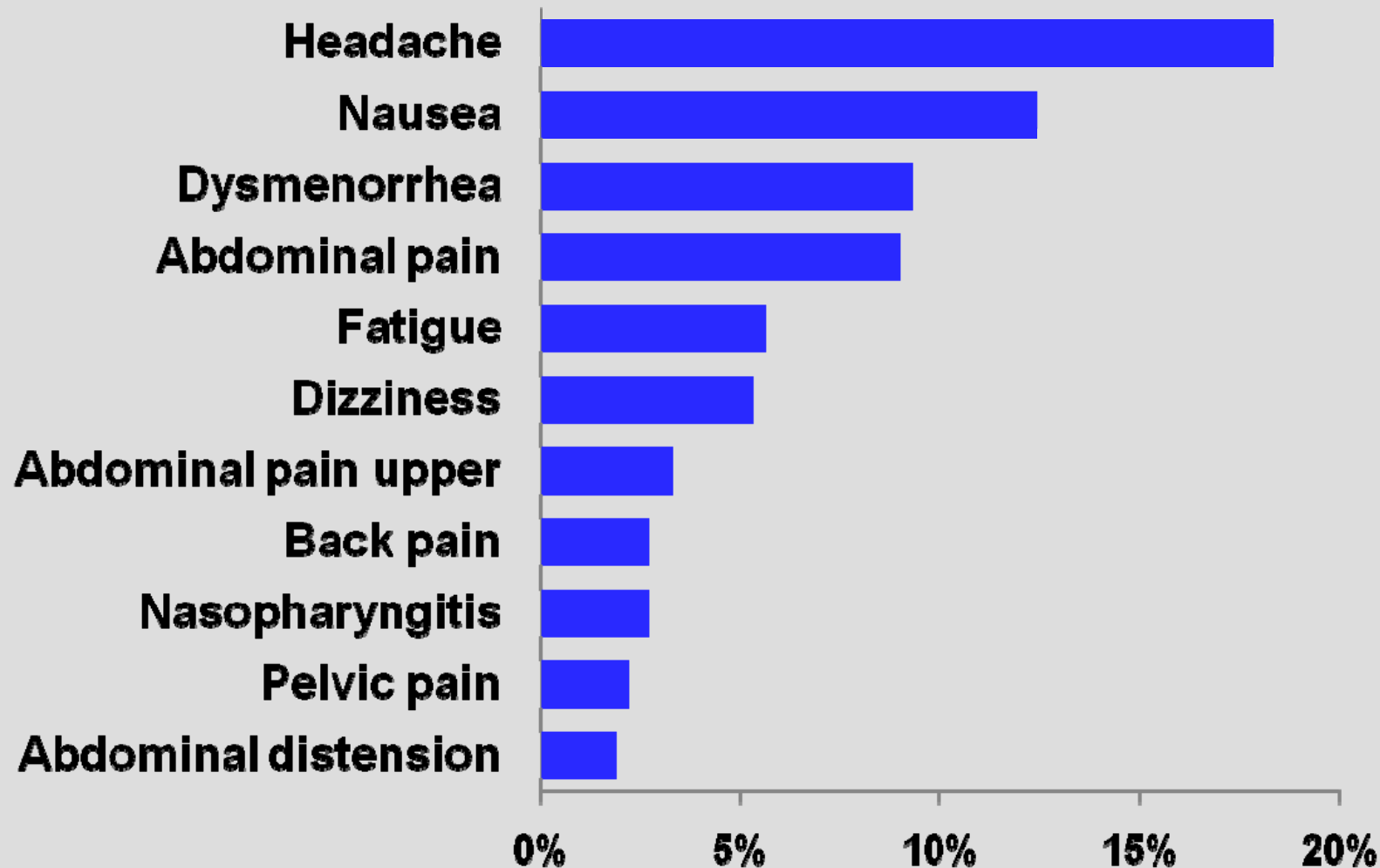
* Assessed by investigator as possibly related; all others considered unrelated.

Safety From Single Dose Exposure

Pooled Phase 3 ITT Population

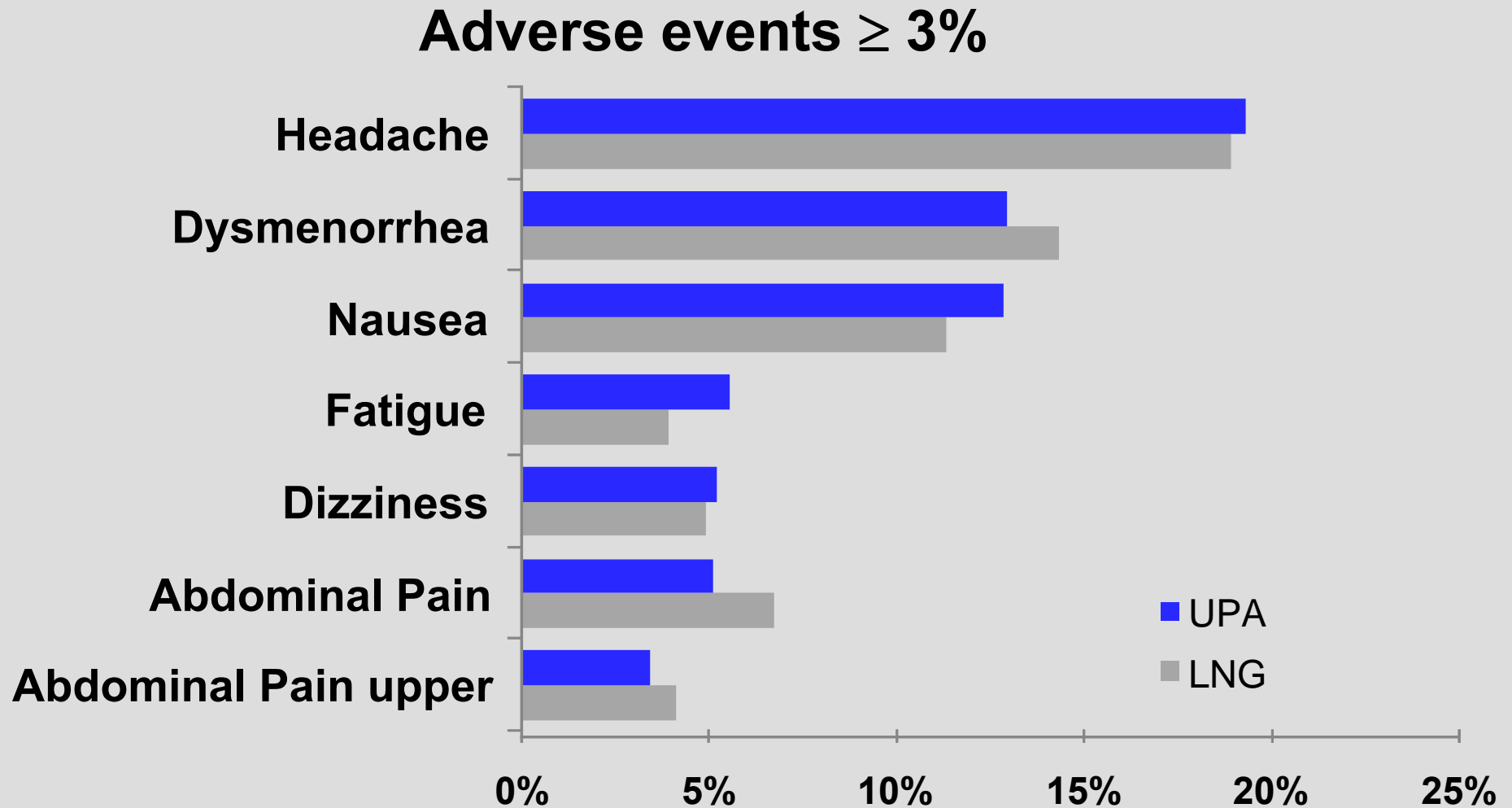
Study 509, 513—Dose 30 mg

Adverse events $\geq 2\%$



AEs vs. Levonorgestrel

Study 513 ITT Population—Dose 30 mg

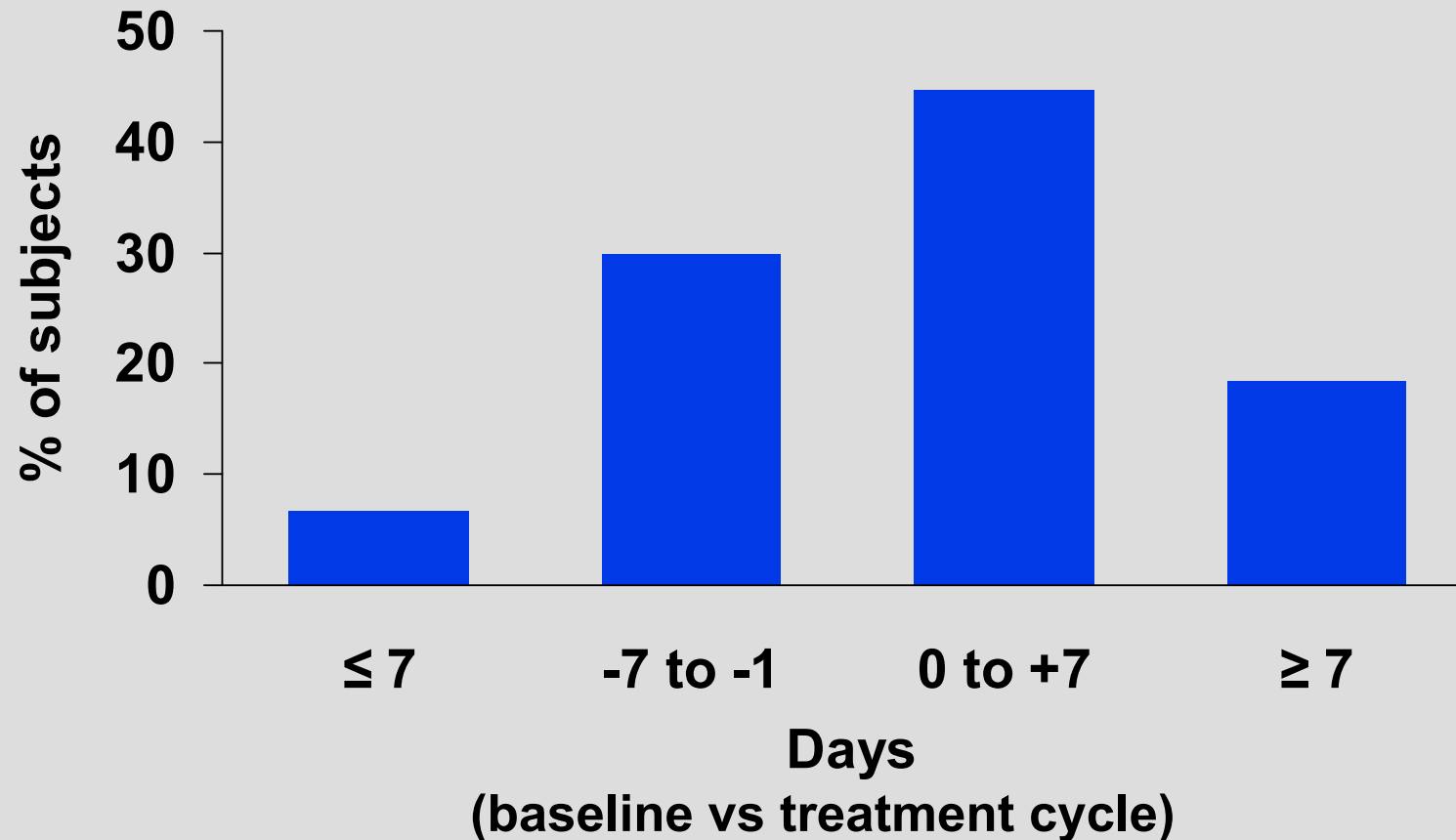


Effects On Menstrual Cycle Length

Pooled Phase 3 ITT Population

Studies 509, 513—Dose 30 mg

Distribution of change in cycle length
Median change: +1 day



Subgroup Analyses

Pooled Phase 3 ITT Population

Studies 509, 513—Dose 30 mg

- ◆ No difference between groups (age, race, BMI, region, concomitant medications)

Adverse reactions	Age				Race			
	< 18	18 - 25	>25 - 35	> 35	White	Black / African Am	Asian	Others
Subjects, n	44	1,722	700	171	1,725	538	48	321
Nausea	9.1	9.3	10.1	5.3	9.9	7.8	8.3	9.0
Headache	6.8	9.2	9.1	6.4	8.4	11.0	8.3	8.7
Dysmenorrhea	2.3	5.3	6.3	1.7	5.5	5.0	4.2	5.0
Abdominal pain (unspec)	0	5.3	6.1	1.7	6.4	3.0	NR	3.7
Fatigue	0	3.7	3.6	1.2	4.1	2.6	4.2	1.6
Dizziness	0	3.4	3.6	1.7	3.4	4.1	2.1	1.9
Upper abdominal pain	0	2.0	2.3	1.7	2.2	1.7	NR	1.9
Pelvic pain	0	1.0	2.1	1.2	1.6	1.1	2.1	NR
Back pain	0	1.1	1.1	1.2	1.1	0.9	2.1	1.2
Vomiting	0	1.2	0.9	0	1.0	1.3	NR	0.3

Ovarian Cysts

Phase 1 Studies—Single Dose Administration

Study	Dose	Size	Subjects, N	Resolution
505	Placebo	15 - 33 mm	2	Spontaneous
	10 mg		1	Rupture
	50 mg		4	Spontaneous
	100 mg		4	Spontaneous for all except one 16 mm cyst persistent at 3 months
506	Placebo	12 - 24 mm	3	Spontaneous
	10 mg		4	
	50 mg		2	
	100 mg		1	

Ovarian Cysts

Phase 1 Study 511—Single Dose Administration

Study	Dose	Maximum Size	Resolution
511	30 mg	52 mm	Persistent follicle Spontaneous collapse at the end of cycle
		30 mm	Luteinized unruptured follicle Spontaneous collapse at the end of the cycle
		31 mm	Pre-ovulatory follicle Normal rupture on cycle day 21

Ovarian Cysts

Phase 2/3 and 3 Studies

Study	Treatment	Subjects, N	Resolution
507	Levonorgestrel 0.75 mg ×2	1	Rupture
509	Ulipristal acetate 30 mg	1	Rupture
513	Levonorgestrel 1.5 mg	1	Rupture*
	Ulipristal acetate 30 mg	1	Rupture

* Reported as an SAE.

Additional Safety Parameters

Single Dose Administration

- ◆ **No clinically relevant abnormalities**
 - Vital signs, biochemistry, hematology
 - Liver function tests
- ◆ **Serum cortisol, prolactin, testosterone:
no change**
- ◆ **Ovarian hormones: effects related to
PR modulation**

Safety From Repeated Dose Exposure

Summary of Findings

Studies 509, 513, 510—Dose 2.5, 5, 10, 30 mg

- ◆ **AE profile for repeat enrollers in Phase 3 similar to overall study population**
- ◆ **In repeat dose Study 510**
 - **TEAE similar in all groups, including placebo**
 - **2 SAEs: abdominal pain (10 mg) and ovarian cyst (5 mg)**
 - **No appreciable variation in lab tests or hormones**
 - **Dose dependent reduction of menstrual bleeding**
 - **Persistent ovarian follicles ≥ 30 mm in some subjects in all groups**

Pregnancy Outcome Overall Clinical Database

**Ulipristal acetate
n = 4,736**

Overall pregnancies

92

**Lost to follow-up
(after pregnancy diagnosis)**

10

Outcome data available

82

Pregnancy Outcome

Study 507 ITT Population—Dose 50 mg

	Ulipristal acetate n = 832	Levonorgestrel n = 840
Number of pregnancies	12	14
Outcome, n (% of pregnancies with known outcome)		
Spontaneous miscarriage	2 (18.2)	5 (35.7)
Elective termination	9 (81.8)	8 (57.1)
Live birth	0	1 (7.1)
Lost to follow-up (after pregnancy diagnosis)	1	0

Pregnancy Outcome

Study 513 ITT Population—Dose 30 mg

	Ulipristal acetate n = 1,104	Levonorgestrel n = 1,117
Number of pregnancies	20	30
Outcome, n (% of pregnancies with known outcome)		
Spontaneous miscarriage	5 (26.3)	5 (17.2)
Elective termination	14 (73.7)	21 (72.4)
Live birth	0	3 (10.3)
Lost to follow-up (after pregnancy diagnosis)	1	1

Pregnancy Outcome

Overall Clinical Database

Ulipristal acetate
n = 4,736

Overall pregnancies	92
Outcome data available	82
Outcome - n (% of pregnancies with known outcome)	
Spontaneous miscarriage	15 (18.3)
Elective termination	60 (73.1)
Live birth	7 (8.5)
Ectopic pregnancy	0

Pregnancy Outcome

Multiple Dose PK Study (Other Sponsor)

Age	Dose / Duration	Treatment Start / Stop	Pregnancy diagnosis	Description	Expected delivery
31 yrs	20 mg 10 days	3 Feb 2010 12 Feb 2010	23 Feb 2010	Uneventful ongoing twin pregnancy	18 Oct 2010

Post-Marketing Safety Experience

- ◆ **Summary of safety surveillance**
 - No new adverse reactions reported
 - No safety signal detected
- ◆ **Pregnancy exposure: 21 pregnancies reported to date**
 - 14 ongoing normal pregnancies
 - 2 confirmed elective terminations
 - 1 miscarriage
 - 4 lost to follow-up

Safety Summary

- ◆ Evaluated in > 4,700 women
 - Single doses up to 200 mg
 - Continuous daily dosing up to 10 mg/d for 84 days
 - >2,700 women with the to-be-marketed 30 mg dose
- ◆ Well-tolerated
 - Most frequently reported AE (headache, nausea, dysmenorrhea, abdominal pain) similar to approved emergency contraceptives
 - Slight increase in menstrual cycle length
- ◆ No significant safety findings
- ◆ Pregnancy exposure data, while limited, do not suggest increased risk of miscarriage

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Safety of Ulipristal Acetate

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Head of Medical Affairs, HRA Pharma

Benefit/Risk and Conclusions

Erin Gainer, PhD, MPH

Benefit Risk and Conclusions

Erin Gainer, PhD, MPH

Benefits

Summary of Evidence

- ◆ **Pharmacology: Potent inhibition of ovulation, even at the peak of the fertile window**
- ◆ **Efficacy: Significant prevention of pregnancy across 4 efficacy trials conducted primarily in the US**
- ◆ **Time window of use: Consistent reduction of pregnancy risk when used up to 120 hrs after intercourse – 2 additional days for intervention in comparison to FDA approved labeling of marketed products**

Risks

Summary of Evidence

- ◆ **Safety: No signals from preclinical or clinical trials different from marketed emergency contraceptives**
- ◆ **AEs: profile similar to marketed products**
- ◆ **Main limitations of safety database: pregnancy exposure**

The benefits clearly outweigh the risks

Strategies and Proposals

Finding

Proposal

Ulipristal acetate is not effective in every case

Ulipristal acetate may lengthen the menstrual cycle

Further unprotected intercourse may lead to pregnancy

High BMI may increase risk of treatment failure

Pregnancy exposure database limited

Advise pregnancy testing if next menstrual period > 1 week late

Counsel on routine contraception for ongoing prevention of pregnancy

Encourage monitoring of high BMI patients to detect failure early

Prescription-only product

Marketed in single-tablet pack with enclosed patient package insert

Strategies and Proposals

Patient Package Insert

- ◆ **Included in each single-tablet pack**
 - Pharmacist does not have to remember to dispense it
 - Every patient will receive one
- ◆ **Easy to read Q&A format**
 - What ella is
 - What ella is not
 - When to take ella
 - When ella should not be taken
 - Most common side effects
- ◆ **Directs patients to medical information hotline**

Strategies and Proposals

Pharmacovigilance

- ◆ **Routine pharmacovigilance complemented by targeted activities**
 - **Facilitate collection of spontaneous reports of exposed pregnancies via a web-based interface**
 - **Use specific report forms for pregnancies**
 - **Consolidate all information on pregnancy exposure in global database**
 - **Convene expert board periodically to review pregnancy outcome data**
 - **Report on results of European PV program regularly**

Overall Conclusions

- ◆ If reducing unintended pregnancy is a goal for public health⁽¹⁾, individual women need contraceptive options
- ◆ When contraception fails or intercourse is not planned, women deserve a second chance to prevent pregnancy
- ◆ Ulipristal acetate potently inhibits ovulation
- ◆ Ulipristal acetate is safe and effective for emergency contraception
- ◆ Ulipristal acetate reduces pregnancy risk when used up to 5 days after intercourse
- ◆ US women deserve this highly effective option

1- <http://www.hhs.gov/secretary/about/reduce.html>

Supporting Slides

Lead follicle final outcome after Treatment

Study 511—30 mg

	UPA (n=34) n (%)	Placebo (n=34) n (%)
Follicle rupture within 5 days post-tx	14 (41.2%)	34 (100%)
Follicle rupture within 6-10 days post-tx	15 (44.1%)	-
Luteinization prior to rupture	2 (5.9%)	-
Luteinized unruptured follicle	3 (8.8%)	-

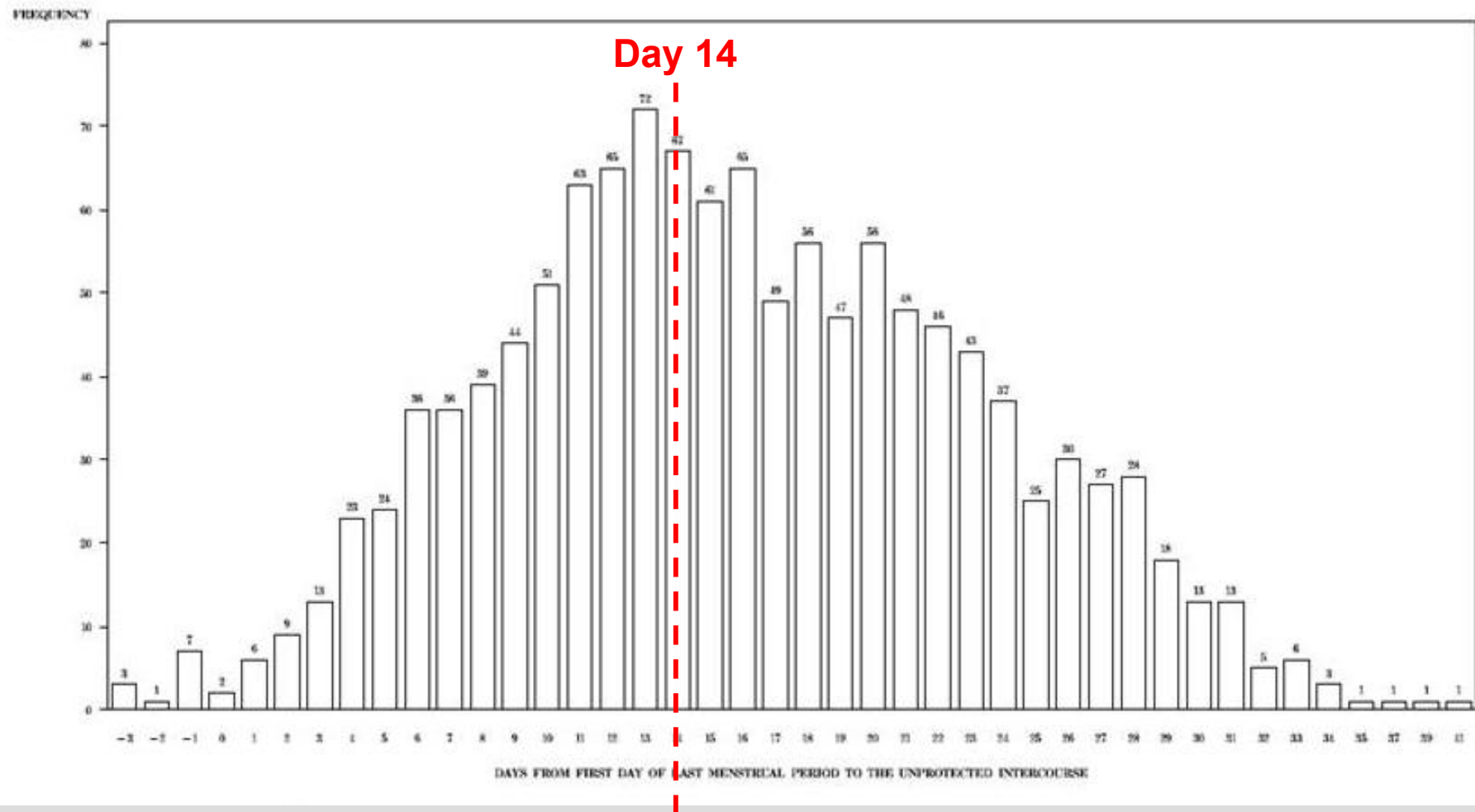
European Label ellaOne (Last Update May 2010)

- ◆ **Special warnings and precautions for use**
- ◆ Concomitant use with an emergency contraceptive containing levonorgestrel is not recommended.
- ◆ Use in women with severe asthma insufficiently controlled by oral glucocorticoid is not recommended.
- ◆ Emergency contraception with ellaOne is an occasional method. It should in no instance replace a regular contraceptive method. In any case, women should be advised to adopt a regular method of contraception.

Distribution of UPIs

Study 509 – mITT Population

FIGURE 3.1 - HISTOGRAM OF DAYS FROM FIRST DAY OF LAST MENSTRUAL PERIOD TO THE UNPROTECTED INTERCOURSE (mITT)



COMPARISON UPA VS LNG BEYOND 72H

Study 513 – mITT Population

Time	Ulipristal Acetate			Levonorgestrel		
	Exposed Subjects	Observed Pregnancies	Observed Pregnancy Rate 95% C.I.	Exposed Subjects	Observed Pregnancies	Observed Pregnancy Rate 95% C.I.
>72 – 120	95	0	0 [0 - 3.81]	102	3	2.94 [0.61 - 8.36]

Note that the upper limit of the exact 95% confidence interval for the ulipristal acetate pregnancy rate is below the untreated expected pregnancy rate and also below 4%

In contrast, the upper 95% confidence limit for levonorgestrel is above both the untreated expected pregnancy rate and 4%.

Ulipristal acetate and mifepristone Receptor binding profiles

Studies 401, 402 & 449

Compounds	Receptor affinity (IC50, nM)					
	PR	hPR-A	hPR-B	GR	ER	AR
Ulipristal acetate	4.2	-	-		6,767	17
	13.5	7.7	6.8	18.2	-	65.5
	13.6	8.5	7.7	15.4	-	-
Mifepristone	3.0	-	-	1.6	946	10
	11.5	9.6	7.8	10.0	-	45.3
	11.5	10.6	9.5	9.1	-	-

UPA and Mifepristone Metabolites – *In Vitro* Activity

◆ *In vitro* activity (IC₅₀, nM)

Compounds	R5020 transcription	R5020 alkaline phosphatase	Dexamethasone transcription
Ulipristal acetate	2.0±0.4	8.2±2.2	73±18
Mono-N-demethylated- UPA	3.2±1.1	4.5±1.8	1,300±100
Didemethylated-UPA	200±60	130±20	2,500±300
Mifepristone	1.3±0.2	7.0±1.3	5.9±1.5
Mono-N-demethylated mifepristone	7.6±1.9	33±13	45±6

Ulipristal Acetate and Mifepristone – Effect On Ovulation In Rats

◆ 4-day cycling rats dosed p.o. at 12.00 on day of pro-estrous

Doses (mg/rat)	Number of ovulating rats	
	Ulipristal acetate	Mifepristone
0 (Vehicle)	16/16	
0.5 ^a	5/8*	6/8
1.0	3/8*	7/8
2.0	0/8*	8/8
4.0	-	4/8*
8.0	-	2/8*

(a) 0.5 mg/rat = 15 mg/m²

*p<0.05 vs. control

Ulipristal acetate & mifepristone – Exposure during gestation in monkeys

◆ Effects on early gestation (GD23-26) in monkeys

Species	Compound	Result
Monkey	Vehicle	2/3 live births
	Ulipristal acetate	0.5 mg/kg/day: 0/5 loss, 4/5 live births, 1/5 stillbirth 5 mg/kg/day ^a : 2/5 loss ^b , 2/5 live birth, 1/5 stillbirth
	Mifepristone	0.5 mg/kg/day: 2/5 loss, 3/5 live birth 5 mg/kg/day: ^a 4/5 loss, 1/5 live birth

(a) 5 mg/kg = 60 mg/m²

(b) Presumably spontaneous loss in 1 animal

GD = gestation day

Ulipristal Acetate & Mifepristone – Exposure During Gestation In Guinea pigs

◆ Effects on late gestation (GD43-44) in guinea pigs

Species	Compound	Result
Guinea-pig	Ulipristal acetate	3 mg/animal: 0/8 loss 10 mg/animals: 3/8 loss 30 mg/animal ^a : 6/8 loss
	Mifepristone	3 mg/animal: 3/8 loss 10 mg/animal: 4/8 loss 30 mg/animal ^a : 6/8 loss

(a) 30 mg/animal = 400mg/m²

GD = gestation day

Comparison Between Ulipristal Acetate and Mifepristone

Models	Parameter	UPA	Mifepristone
Inhibition of ovulation in rats (single dose on proestrus)	MED (mg/rat p.o)	0.5	4
Effects in monkeys (dosing GD23-26)	MED (mg/kg p.o)	5	0.5
Effects in guinea pigs (dosing GD43-44)	MED (mg/g-pig s.c)	10	3

EU Pharmacovigilance Program

Prescriber-Based Observational Study

Outline of Draft Protocol under Discussion with EMA

◆ Objective

- To assess clinical follow-up and outcomes of pregnancies resulting from ellaOne failure or pregnancies inadvertently exposed to ellaOne

◆ Design

- Prospective multicenter observational study

◆ Investigators

- 1000 prescribers in multiple European countries (France, Germany, Italy, Spain and UK)

EU Pharmacovigilance Program

Prescriber-Based Observational Study

Outline of Draft Protocol under Discussion with EMA

◆ Study population

- Pregnant women (≥ 16 yr in UK and ≥ 18 yr in France, Germany, Italy and Spain) exposed to ellaOne
 - during the menstrual cycle in which the pregnancy started or
 - at any time during pregnancy

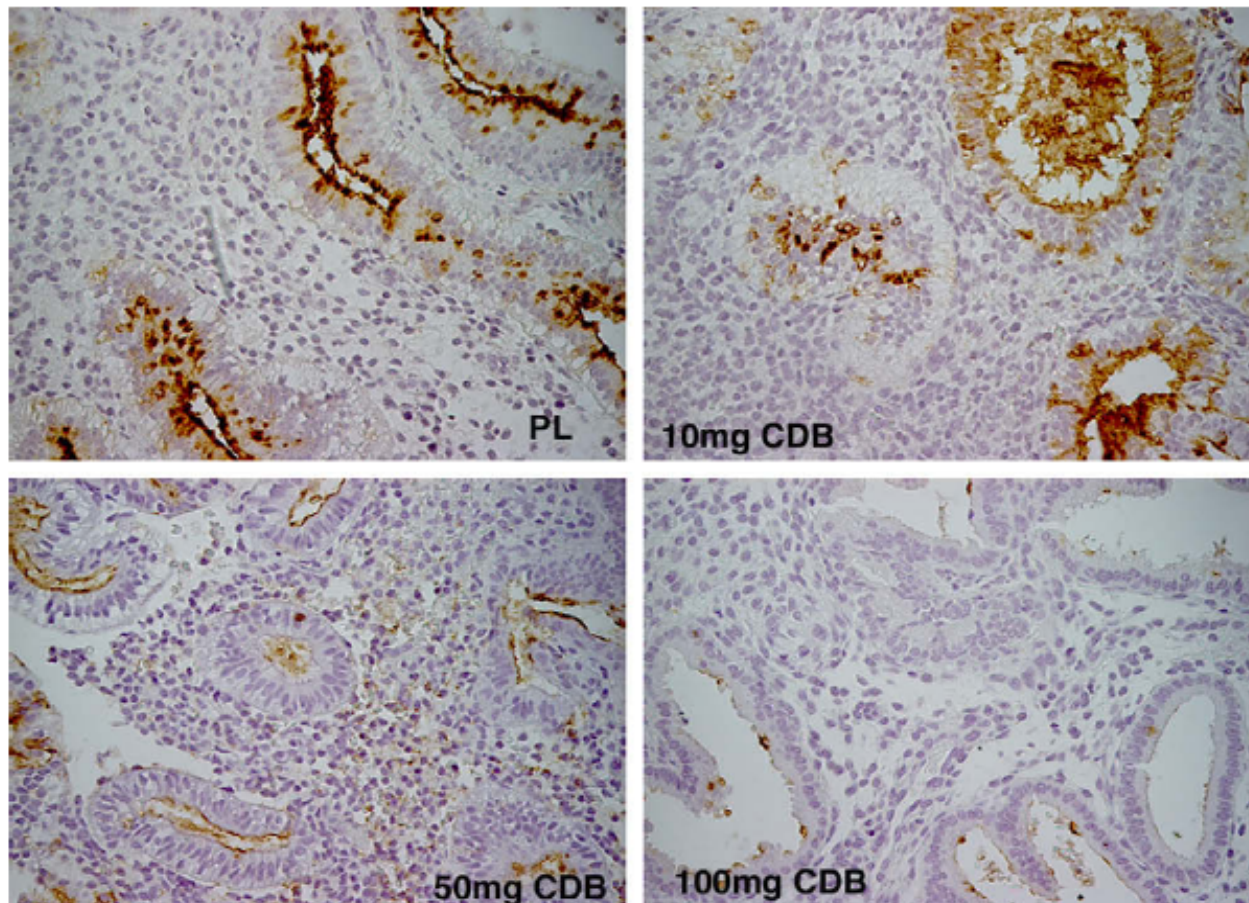
◆ Primary data collected

- Detailed clinical data on pregnancy course and pregnancy outcome

Early luteal Phase Administration

Study 506—10, 50, 100 mg

Representative endometrial MECA-79 immunohistochemistry in biopsy specimens from women receiving placebo (PL) and 10, 50, and 100 mg CDB-2914. The H score was significantly reduced in the 50- and 100-mg groups compared with placebo ($P < .001$).



European Label ellaOne (Last Update May 2010)

◆ Pregnancy

- ◆ ellaOne is contra-indicated during an existing or suspected pregnancy.
- ◆ Extremely limited data are available on the health of the foetus/new-born in case a pregnancy is exposed to ulipristal acetate. Although no teratogenic potential was observed, animal data are insufficient with regard to reproduction toxicity.
- ◆ HRA Pharma maintains a pregnancy registry to monitor outcomes of pregnancy in women exposed to ellaOne. Patients and health care providers are encouraged to report any exposure to ellaOne by contacting the Marketing Authorisation Holder.

ellaOne® Pregnancy Registry

HRA Pharma

Home

Patient

Health Care provider

Language

Welcome to ellaOne® Pregnancy Registry

This pregnancy registry is developed by HRA Pharma. It is aimed at collecting medical data about pregnancy outcomes in women exposed to ellaOne®.

If you want to obtain general information on the Pregnancy Registry or on ellaOne®, please click on 'Patient' below.

If you are a health care provider, please click on 'Health Care Provider' below to read information on this registry and access to the report forms you will need to fill in and send to HRA Pharma.



PATIENT

HEALTH CARE
PROVIDER

HRA Pharma: Who are we?

HRA Pharma is an emerging European pharmaceutical company that designs products, devices and supporting services in the fields of reproductive health and endocrinology and makes them available to doctors and patients worldwide.

Headquartered in Paris, France with local teams based at subsidiaries in Germany (Bochum), Italy (Rome), Spain (Madrid), the United Kingdom (London) and the United States (New York City), HRA Pharma has forged a strong network of Research and Development, manufacturing, distribution and Non Governmental Organizations partners which enables it to satisfy critical patient needs and improve patient health in over 60 countries across the globe.

For more information on HRA Pharma, please consult our website: <http://www.hra-pharma.com>

How is patient's confidentiality ensured?

Patients' and babies' identities will not be collected. The pregnancy registry will only collect patients' initials and dates of birth that will allow HRA Pharma to obtain information on a patient correctly identified when contacting health care professionals.

How can you participate?

When you are advised that one of your patients has been inadvertently exposed to ellaOne® during her pregnancy or has become pregnant despite having taken ellaOne® following unprotected intercourse, you are encouraged to report prenatal exposure to ellaOne® during pregnancy as early as possible to facilitate the collection of prospective and unbiased information.

The report forms (detailed below) should be printed, completed, signed and sent via mail, email or, preferably, by fax to:

► **HRA Pharma**
15, rue Béranger
75003 PARIS
FRANCE
Fax: 00 33 1 42 77 03 52
Email: pharmacovigilance@hra-pharma.com

Enrolling a patient in the registry will involve completing the following report forms:

The **Enrolment Form** is the first form to be completed. This form is mainly intended to collect data on pregnancy diagnosis and exposure to ellaOne®:



Enrolment form - 80 ko - PDF format

The **Pregnancy Outcome Form** has to be completed once you know the pregnancy term / termination:



Pregnancy outcome form - 32 ko - PDF format

NB: In case of serious adverse event including safety issues with foetus or newborn baby, **Additional Forms** will have to be completed.

From <http://www.ellaone-registry.com>

ENROLLMENT FORM

Please return this form by fax to HRA Pharma at + 33 1 42 77 03 52

You have identified a patient potentially exposed to ellaOne® during pregnancy. Please complete this enrollment form as well as the pregnancy outcome form for all cases. Depending on the pregnancy outcome, additional specific forms may be applicable.

PATIENT ID

Initials		Date of birth (DD/MM/YY)	
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PREGNANCY INFORMATION

Date of diagnosis	
Date of last menstrual period	
Expected delivery date	

ellaOne® EXPOSURE

Date of ellaOne® intake	
Total dose administered (30 mg per tablet)	
Time from intercourse to ellaOne® intake (hours)	
Pregnancy stage at ellaOne® exposure	<input type="checkbox"/> Before pregnancy (treatment failure) <input type="checkbox"/> 1st trimester <input type="checkbox"/> 2nd trimester <input type="checkbox"/> 3rd trimester
Pregnancy status before ellaOne® intake	<input type="checkbox"/> Not pregnant <input type="checkbox"/> Pregnant

If the pregnancy outcome is known at this time, please complete the 'pregnancy outcome' form

HEALTH CARE PROVIDER INFORMATION

Last name:	First name:
Medical Specialty:	Affiliation:
Address:	
Country:	
Phone:	Fax:
E-mail:	

Date:	Signature:
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As per the EU Directive 95/46/EC requirements on data protection, you have the right to access and amend the information collected processed by HRA Pharma in the framework of the ellaOne® Pregnancy Registry.

To exercise this right, please:

Send an email to ellaone-pharma.com or

Send a fax to +33 1 40 33 12 31 or

Contact us by phone + 33 1 40 33 11 30