

La place des SPRMs en Gynécologie Médicale

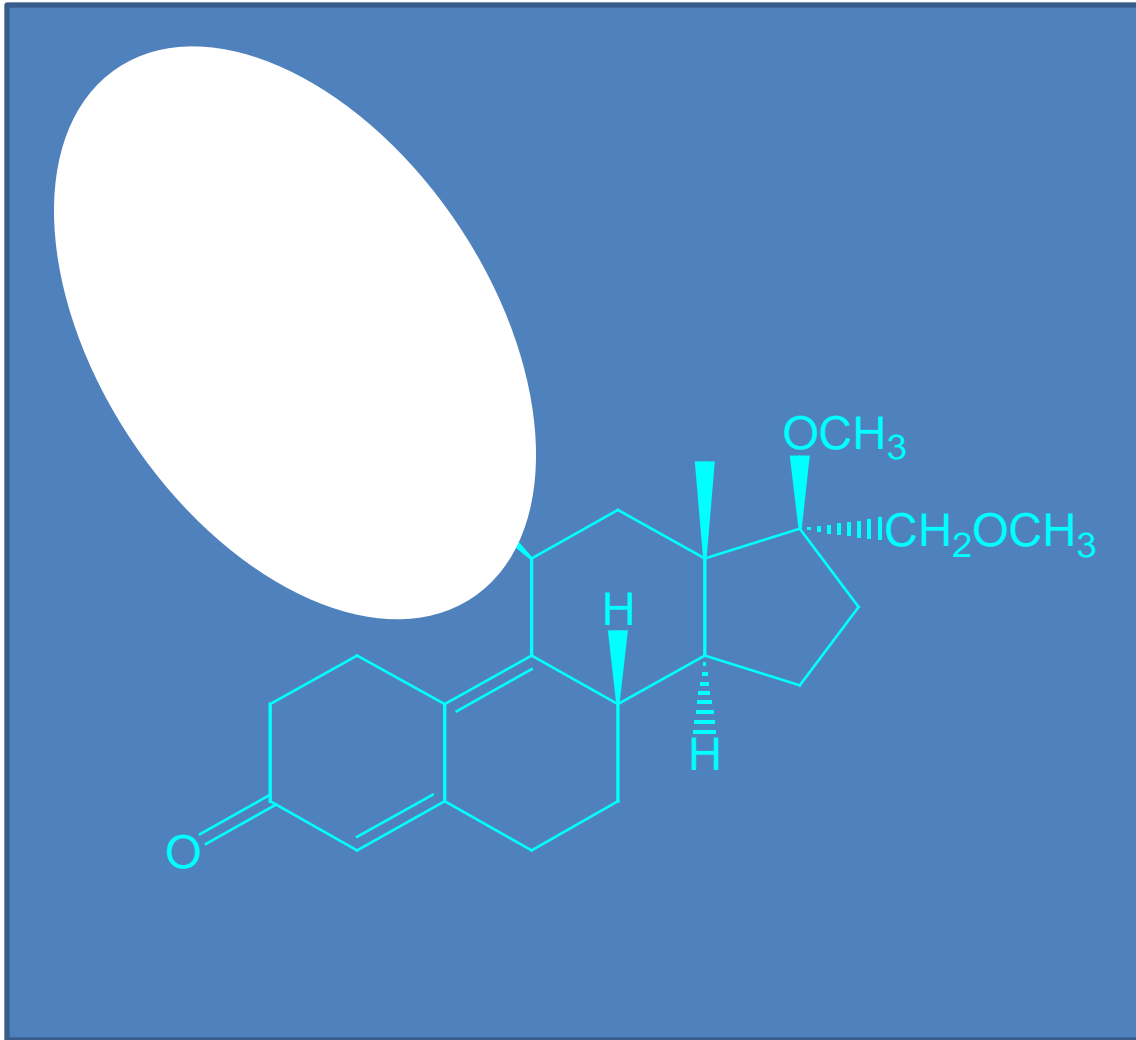
14eme congres Genesis

Paris 23 Septembre 2011

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Service de Gynécologie Obstétrique
Médecine de la Reproduction

Antiprogestatifs / SPRMs



Composé: DCI, Nom commercial® (code développement)	Laboratoire	Etudes : phase et champs d'application
Asoprisnil (J867)	Schering /TAP (USA)	Phase II-III: fibromes
Ulipristal(VA 2914) (PGL 4001) (CDB- 2914) EllaOne® Esmya®	HRA Pharma (France) Preglem (Suisse) NIH (USA)	Contraception d'urgence Phase II: contraception, fibromes (oral and DIU)
Mifepristone, Mifegyne®, (RU 38 486)	Excelgyn (France) Danko (USA)	Interruption de grossesse, contraception d'urgence, fibromes. Phase I-III: contraception, cancer du sein.
Proellex® (CDB 4124)	Repros (USA)	Phase II-III: fibromes, endometriose
ZK230211	Schering (Allemagne)	Phase I-II: hémorragies fonctionnelles, fibromes (DIU)

Indications obstétricales

- **Interruption médicamenteuse de grossesse intra-utérine évolutive.**
En association séquentielle à un analogue des prostaglandines, au plus tard au 63^e jour d'aménorrhée.
- **Ramollissement et dilatation du col utérin en préparation à l'interruption chirurgicale de grossesse du premier trimestre.**
- **Préparation à l'action des analogues des prostaglandines dans l'interruption de grossesse pour raison médicale au-delà du premier trimestre.**
- **Induction du travail lors de mort foetale in utero : lorsque les prostaglandines ou l'ocytocine ne peuvent être utilisées.**
-

Administration à court terme

- Contraception d'urgence: mifepristone (dans 30 pays hors France) et ulipristal acetate (Ella one[®])
- contrôle du saignement induit par les progestatifs
- contrôle de la lutéinisation prématurée en FIV?

Ulipristal vs levonorgestrel

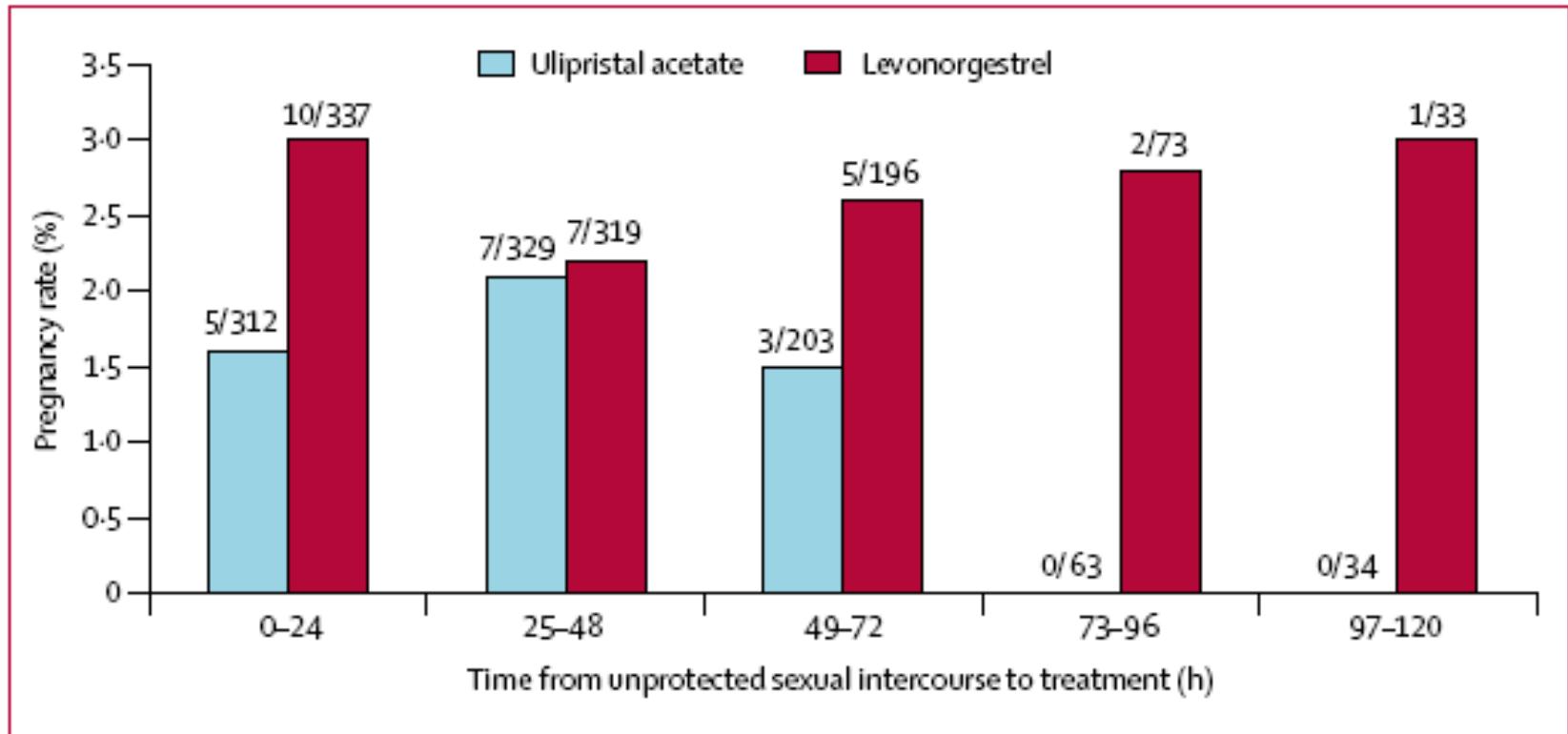


Figure 2: Pregnancy rates according to time from unprotected sexual intercourse to intake of emergency contraception (efficacy-evaluable population)
n/N is shown at the top of each column.

Ulipristal vs levonorgestrel

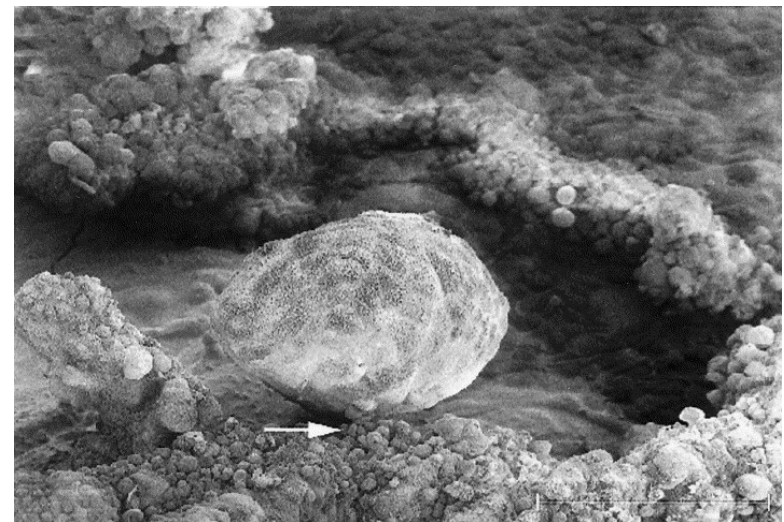
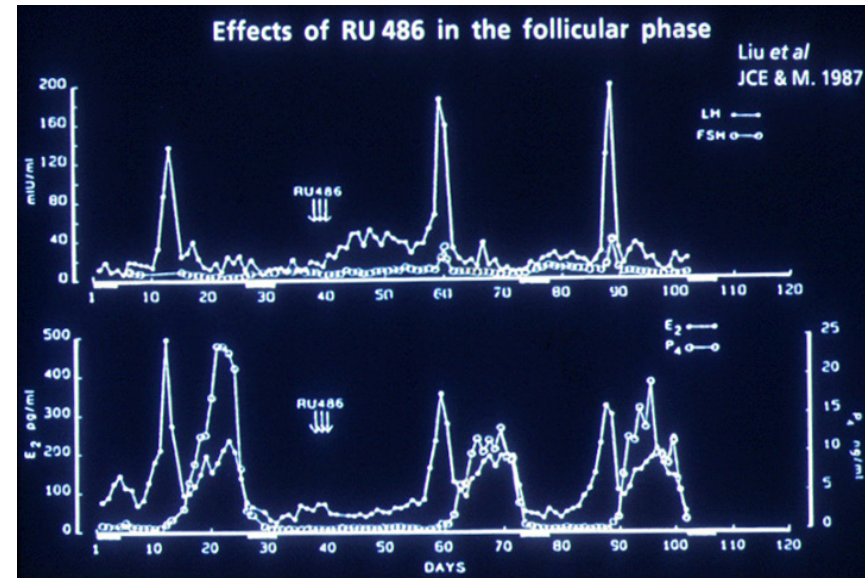
	Pregnancies, n/N (%)		Odds ratio (95% CI)*	p value*
	Ulipristal acetate	Levonorgestrel		
Creinin et al ¹⁸ (0-72 h)	7/773 (0.9%)	13/773 (1.7%)	0.50 (0.18-1.24)	0.135
Current study (0-120 h)	15/941 (1.6%)	25/958 (2.6%)	0.57 (0.29-1.09)	0.091
Meta-analysis (0-24 h)	5/584 (0.9%)	15/600 (2.5%)	0.35 (0.11-0.93)	0.035
Meta-analysis (0-72 h)	22/1617 (1.4%)	35/1625 (2.2%)	0.58 (0.33-0.99)	0.046
Meta-analysis (0-120 h)	22/1714 (1.3%)	38/1731 (2.2%)	0.55 (0.32-0.93)	0.025

*Inferential statistics based on the logistic regression model including significant covariates and the study factor.

Table 2: Efficacy of emergency contraception in single studies and meta-analysis, according to time from unprotected sexual intercourse to intake of emergency contraception (efficacy-evaluable population)

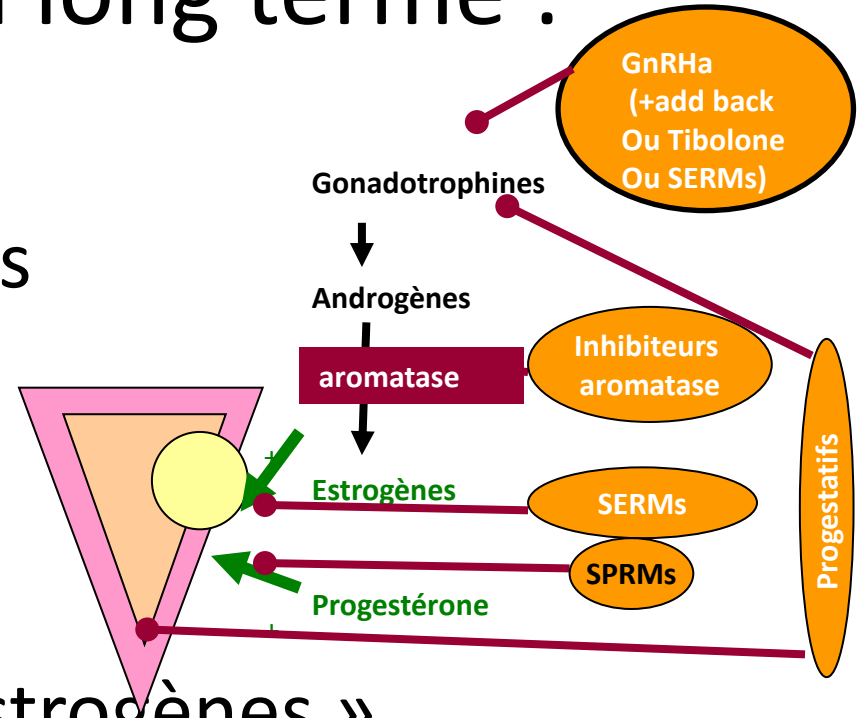
Contraception d'urgence

- Blocage (décalage) du pic de LH
- Retard de la survenue des règles
- Effet endométrial direct interférant avec l'implantation?
(Modèle animal (Banazack 2000)
ou in vitro (Petersen 2005, Lalitkumar 2007))



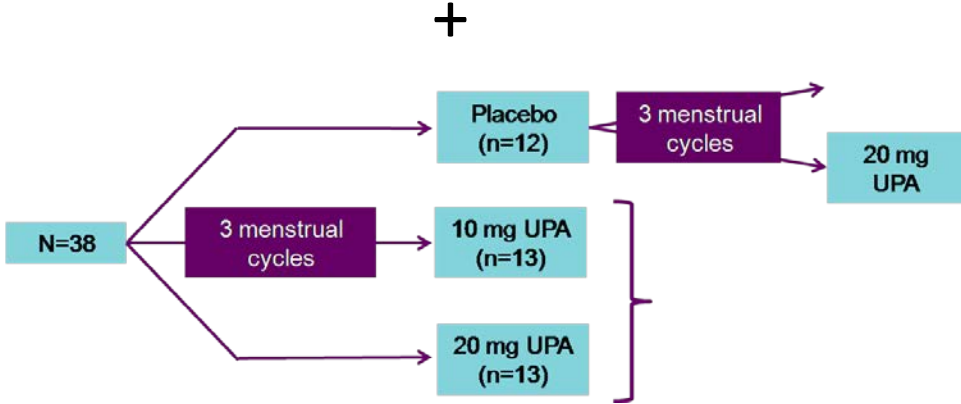
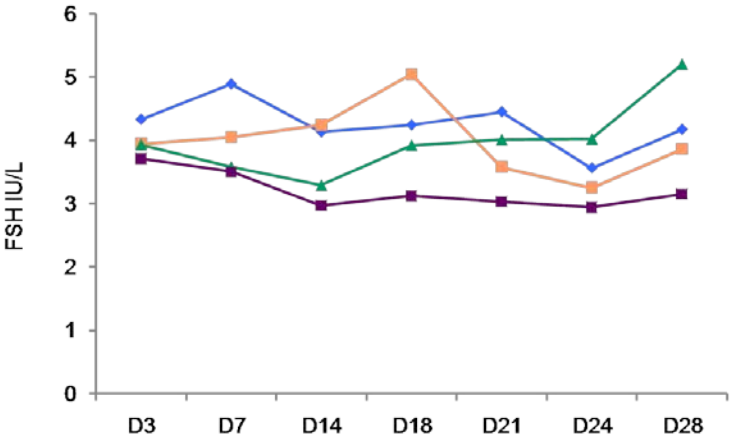
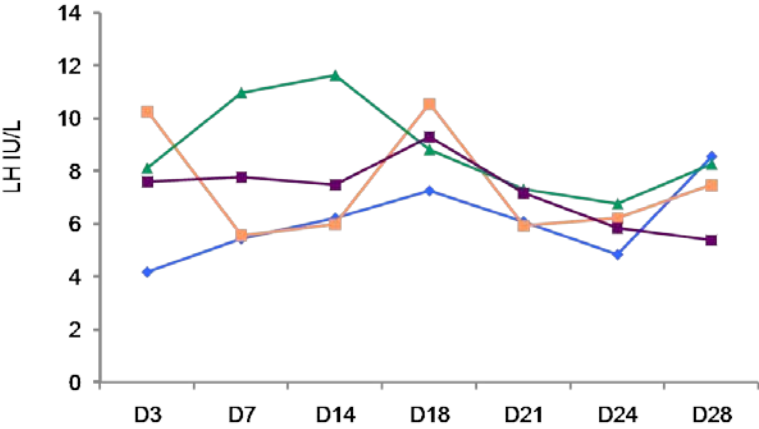
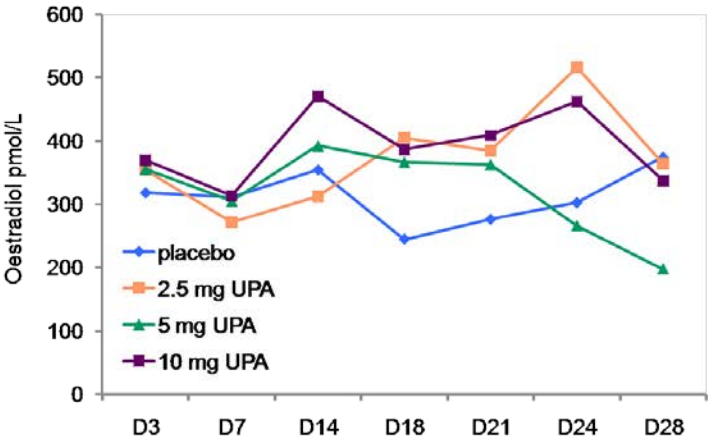
Applications à long terme :

- Traitement des fibromes



- Contraception « sans estrogènes »
- Endometriose
- Cancer du sein (traitement/prévention)

Etude VA 2914 002



Nieman, Chabbert-Buffet & Bouchard
ECE Prague 2010

Effets endométriaux : aménorrhée

Study A				
Treatment groups*	Phase 1		Phase 2	
Amenorrhoea, n	23/26		11/12	
mITT** population, study B				
Treatment groups	Placebo (n=11)	UPA 2.5 mg (n=11)	UPA 5 mg (n=11)	UPA 10 mg (n=10)
Anovulation, %	0.0	9.1 NS	81.8 $p < 0.001$	80.0 $p < 0.001$
Amenorrhoea, n				
TC1	0	3	7	8
TC2	0	4	9	9
TC3	0	2	9	9

Nieman, Chabbert-Buffet & Bouchard
ECE Prague 2010

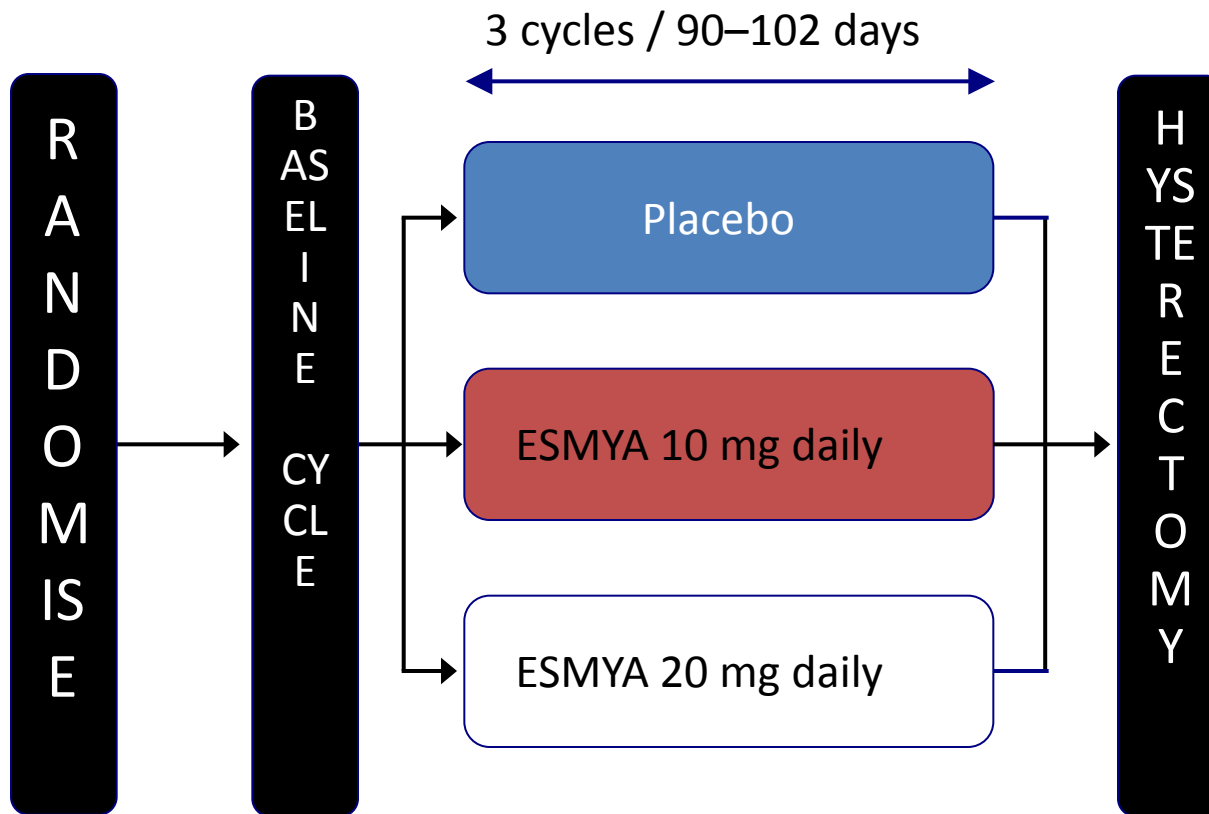
SPRMs et fibromes

- SPRMs inhibent la prolifération et induisent l'apoptose dans les modèles de culture cellulaire fibromateuse mais pas dans les cll myométriales normales (Maruo et al)
- les SPRMs modulent la synthèse du collagène dans les cell myomateuses et non dans les cell myometriales normales

SPRMs et fibromes

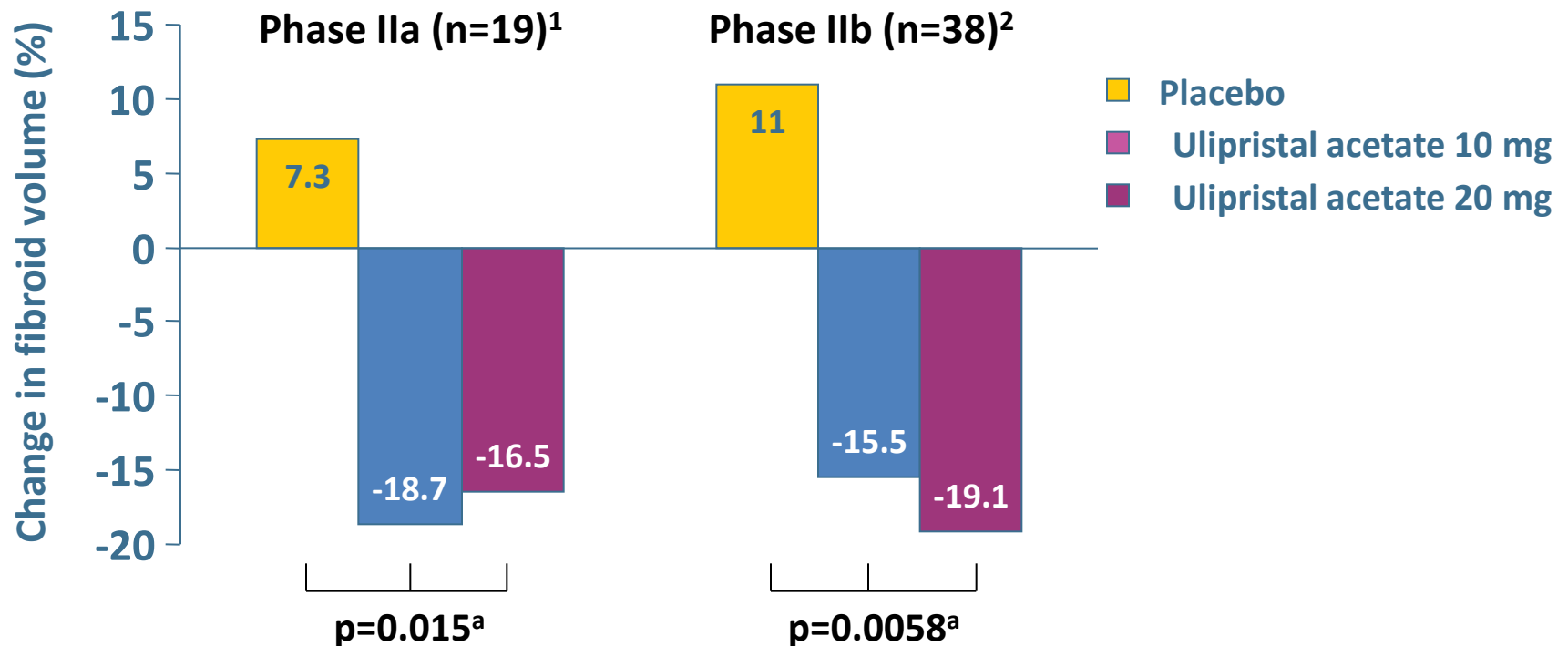
- Mifepristone : plusieurs études de 3 à 6 mois , deux au delà (12 ou 18 mois). Recherche de la dose minimale efficace. Sécurité endométriale.
- Asoprisnil une étude récente (RCT) de trois mois sur 36 femmes
plusieurs autres dont une de 18 mois (166 femmes) et une de 12 mois (250 femmes), terminées non publiées
- CDB 2914/PGL 4001 :
deux études au NIH petit effectif efficacité
deux études randomisées vs GnRH analogue (400 x 2 femmes) 6 mois

Phase IIa study treatment



Ulipristal acetate reduces fibroid size compared with placebo

Mean change in total fibroid volume from baseline after treatment for 3 months



- More patients achieve a reduction in fibroid size with ulipristal acetate than with placebo

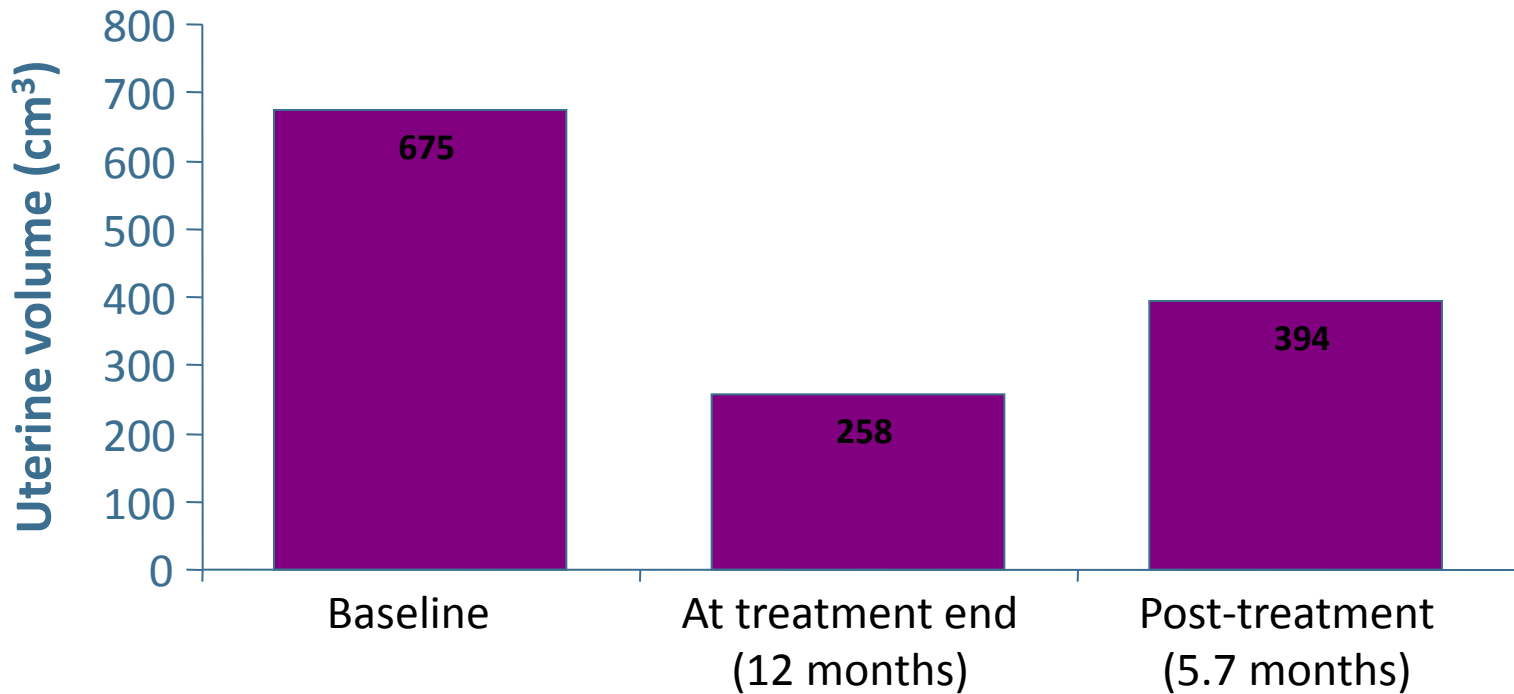
^aCombined ulipristal acetate arms vs placebo

1. Levens et al. Obstet Gynecol 2008;111:1129–1136;

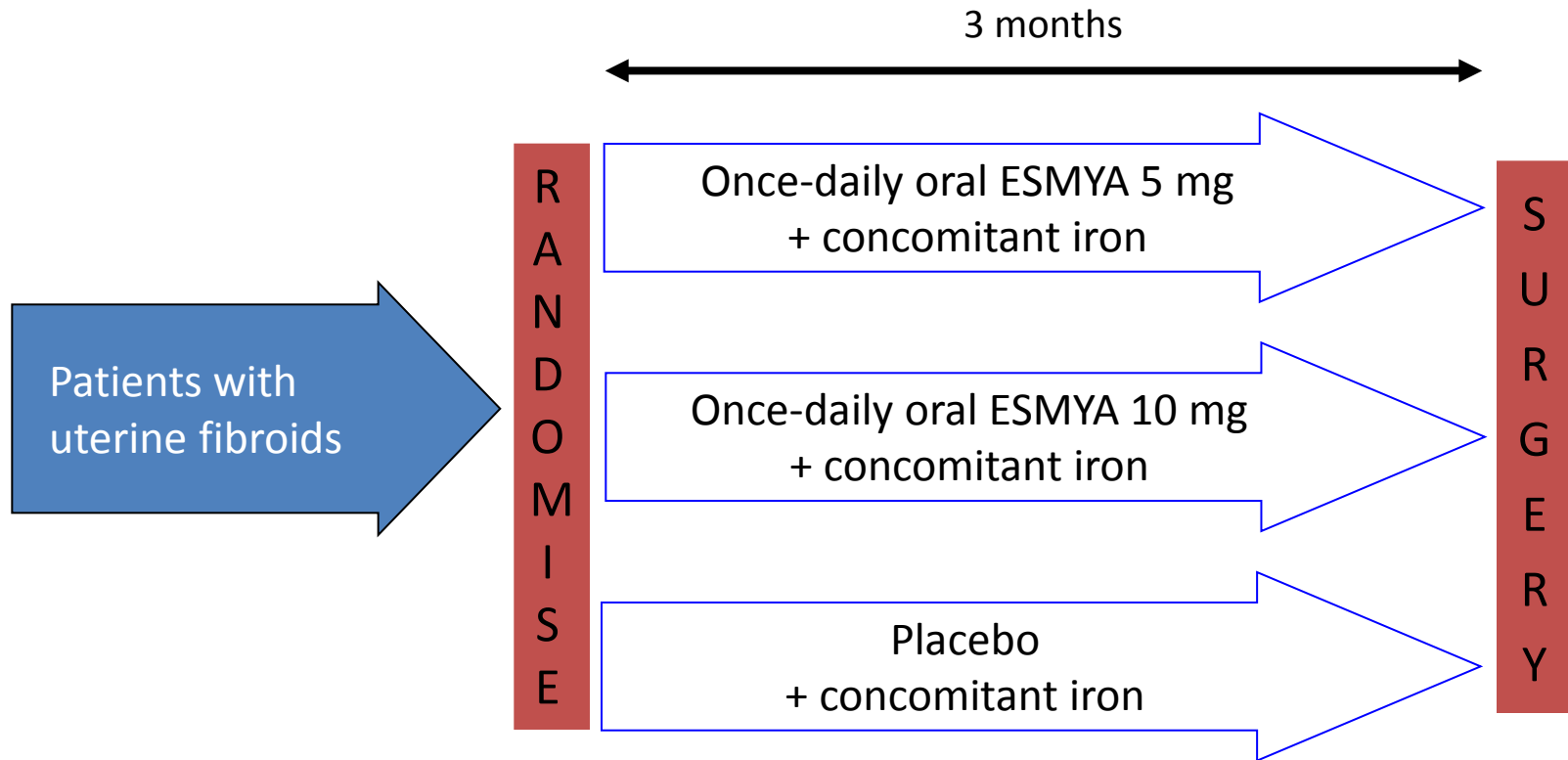
2. Nieman et al. ESG 2009

Beneficial effects of mifepristone is maintained after treatment cessation

Mean uterine volume in women treated for uterine myoma with mifepristone (5 or 10 mg) for 12 months

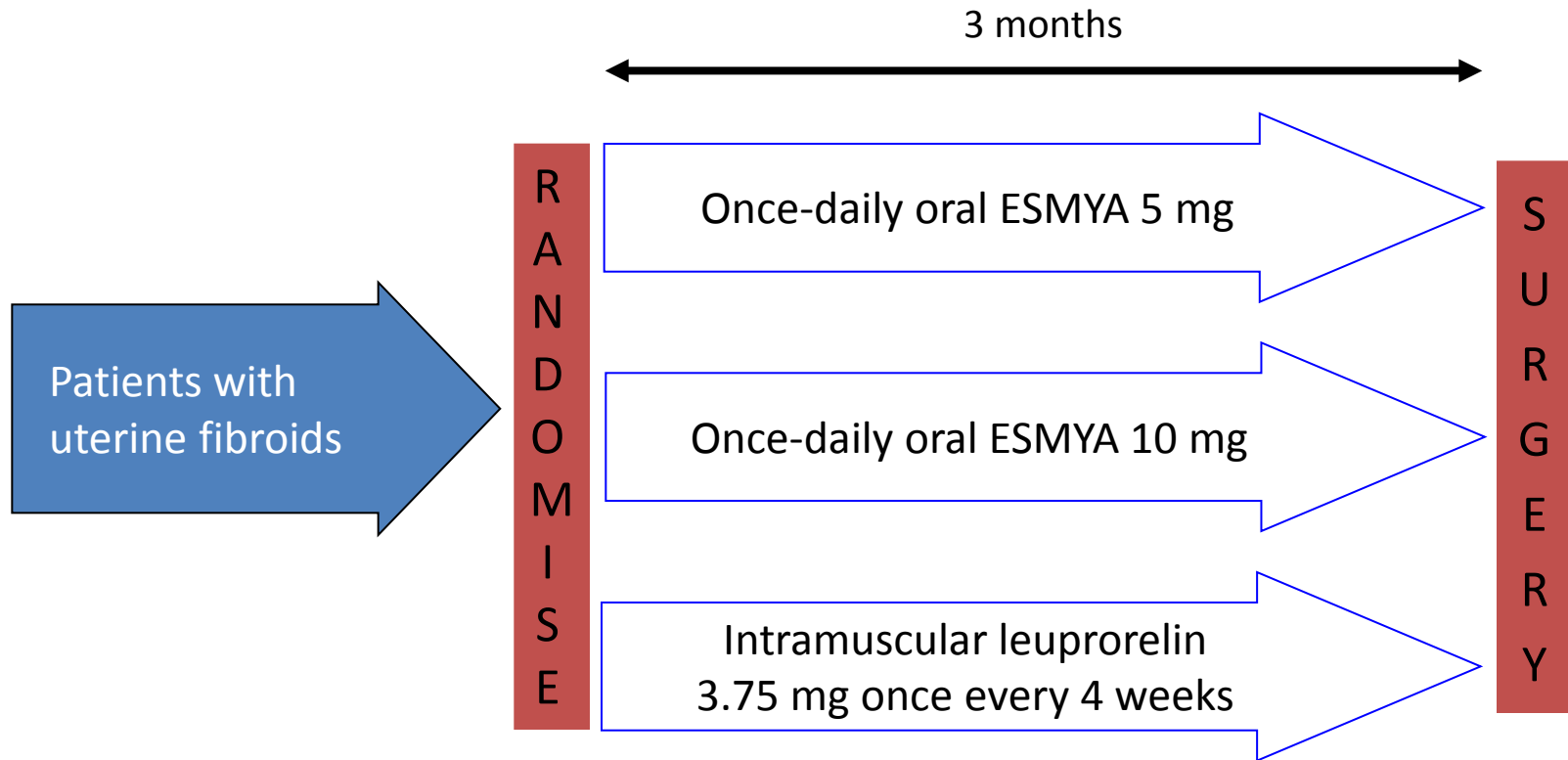


PEARL I: Randomised, double-blind Phase III trial of ESMYA vs placebo



ClinicalTrials.gov Identifier: NCT00755755

PEARL II: Randomised, double-blind Phase III trial of ESMYA vs GnRHa



ClinicalTrials.gov Identifier: NCT00740831

PEARL I and PEARL II: Conclusions

PEARL I

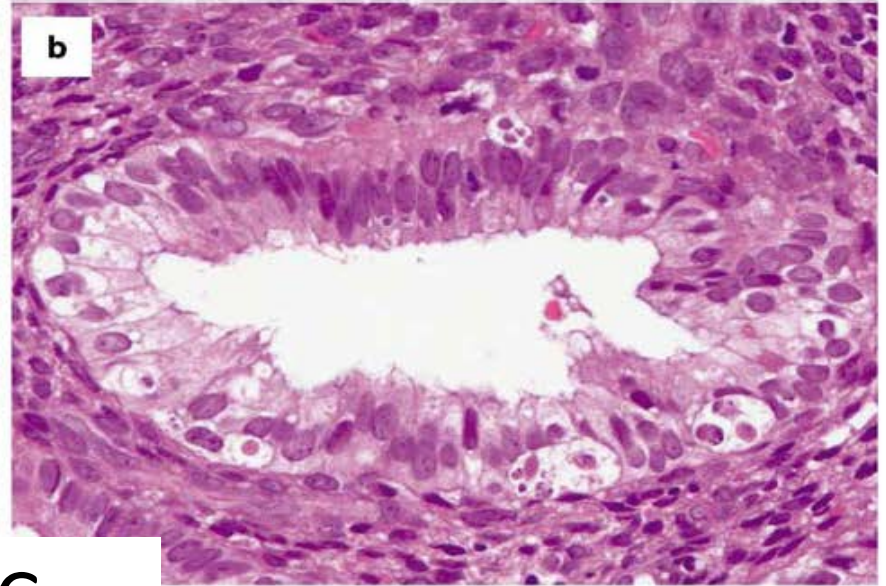
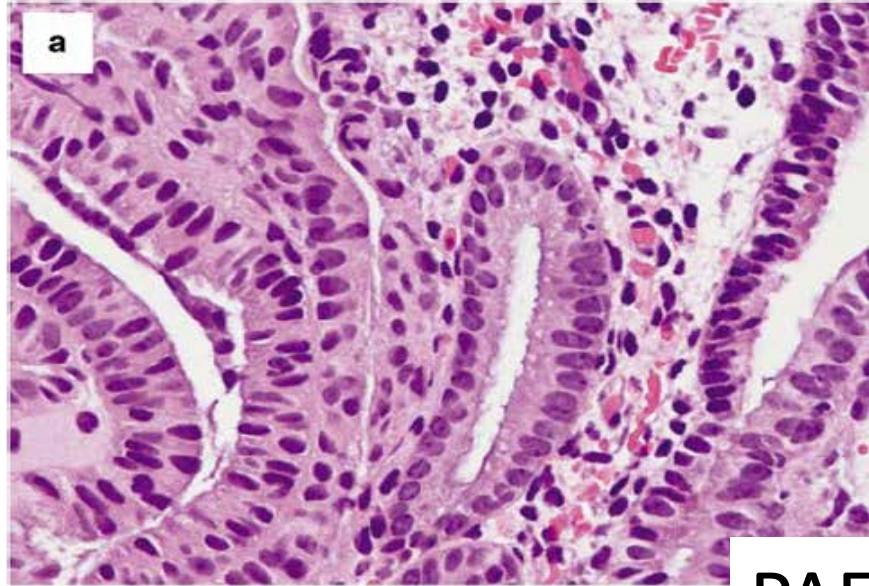
- The study met its two co-primary efficacy endpoints
- Esmya demonstrated statistically significant superior efficacy to placebo in reducing excessive uterine bleeding measured as a percentage of patients with a reduction of PBAC (Pictorial Blood Assessment Chart) score lower than 75 and in reduction of total fibroids volume assessed by centralised MRI reading.
- Esmya also showed superior efficacy to placebo in correcting anaemia caused by uterine fibroids and suppressing fibroids-related pain using the McGill Short Form questionnaire (SF-MPQ). Both the PBAC and SF-MPQ are validated self-reporting tools

PEARL II

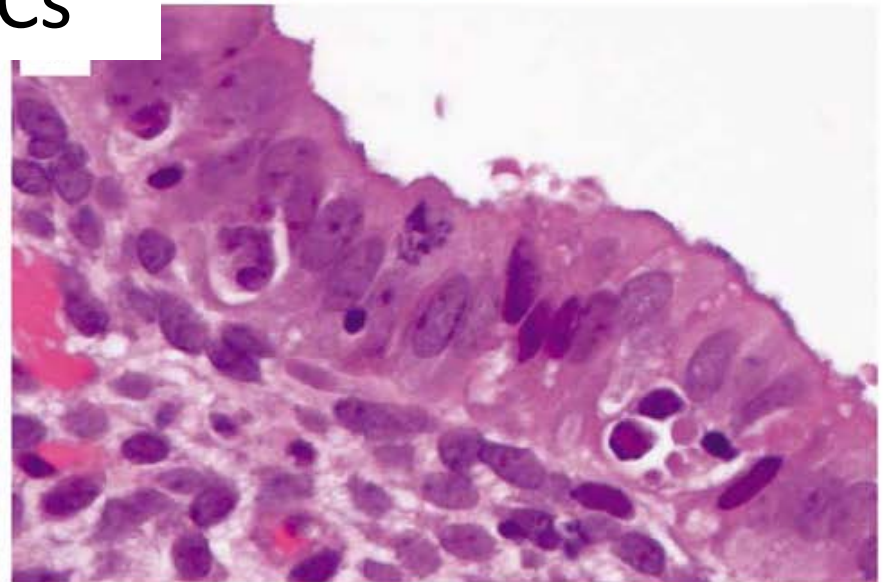
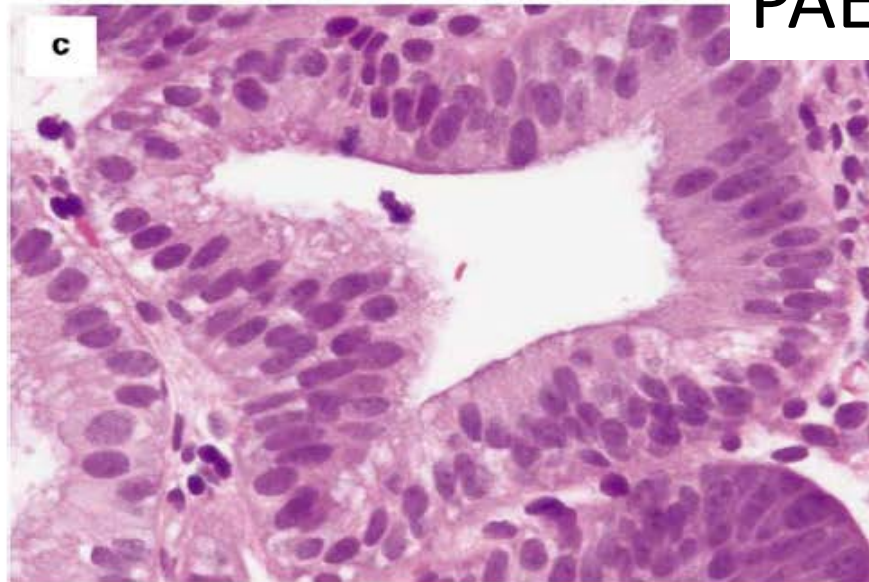
- The study met its primary efficacy and safety endpoints.
 - Esmya met the pre-defined, non inferiority efficacy endpoint versus Leuprorelin to reduce excessive uterine bleeding caused by uterine myomas. The primary endpoint was change from baseline in the bleeding intensity score. This was measured as a percentage of patients with a reduction of PBAC (Pictorial Blood Assessment Chart) score to lower than 75 after 3 months of treatment.
 - Esmya demonstrated superior safety and tolerance with statistical significance versus Leuprorelin regarding castration-related symptoms and their consequences. The principal parameters were serum oestradiol levels and hot flushes.

PregLem to submit a Marketing Authorisation Application (MAA) for Esmya to the European Medicines Agency (EMA) by the end of 2010

Effet endométrial des PRMs

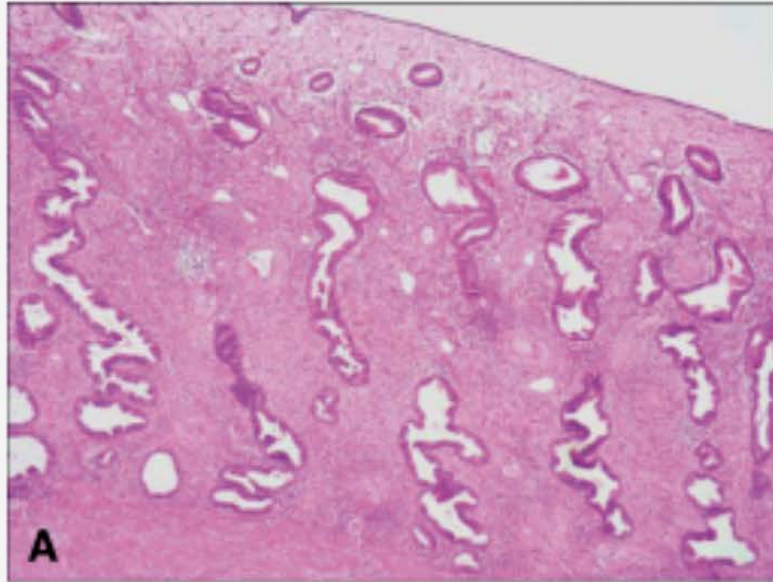


PAECs

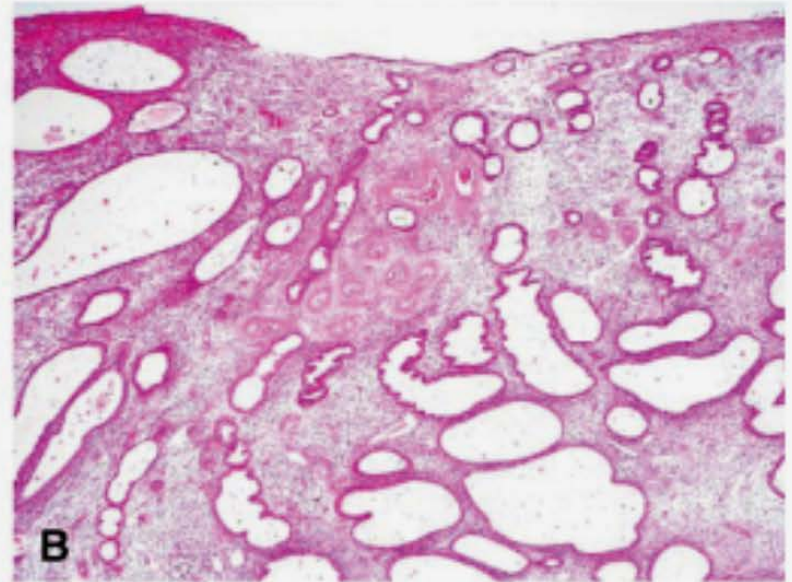


Aspect kystique dilaté

Ph Lutéale



Asoprisnil



Modifications endometriales “non physiologique”

Major Class	Treatment Group				
Subclass	Placebo	PGL4001 2.5mg	PGL4001 5mg	PGL4001 10mg	Total
Additional Description	(Dx=32)	(Dx=32)	(Dx=44)	(Dx=20)	(Dx=128)
Other observations					
Non-physiological:	1 (3.1%)	8 (25.0%)	19 (43.2%)	10 (50.0%)	38 (29.7%)
Epithelial changes present:	1 (3.1%)	5 (15.6%)	11 (25.0%)	6 (30.0%)	23 (18.0%)
Secretion	1 (3.1%)	3 (9.4%)	6 (13.6%)	3 (15.0%)	13 (10.2%)
Mitoses	1 (3.1%)	2 (6.3%)	7 (15.9%)	4 (20.0%)	14 (10.9%)
Apoptosis	1 (3.1%)	3 (9.4%)	6 (13.6%)	4 (20.0%)	14 (10.9%)
Extensive cyst formation	0	6 (18.8%)	15 (34.1%)	9 (45.0%)	30 (23.4%)
Unusual vascular changes present:	1 (3.1%)	1 (3.1%)	5 (11.4%)	1 (5.0%)	8 (6.3%)
Chicken wire capillaries	1 (3.1%)	0	3 (6.8%)	1 (5.0%)	5 (3.9%)
Thick walled vessels	0	0	1 (2.3%)	0	1 (0.8%)
Ectatic vessels	0	1 (3.1%)	2 (4.5%)	1 (5.0%)	4 (3.1%)
Other	0	0	0	0	0

Actuellement contraception/fibrome

Disponible : acétate d'Ulipristal en
contraception d'urgence
(action prolongée / levonorgestrel, \pm plus
importante)

Délivrance sur ordonnance

Remboursement 65%

En voie de commercialisation:
Traitement préopératoire des fibromes
(intérêt de l'absence de carence estrogénique)

En voie de développement
Nouvelles galéniques (DIU, anneaux)
Nouveaux schémas d'administration

