Ulipristal Acetat-
Effekt på myomrelaterad blödning

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ESMYA (UPA) – A SELECTIVE PROGESTERONE RECEPTOR MODULATOR (SPRM)

- Progesterone receptor ligands can possess activity ranging from pure antagonist activity through mixed antagonist/agonist activity to pure agonist activity

- SPRMs are progesterone receptor ligands with mixed antagonist/agonist activity

RU-486 (Mifepristone)  
Ulipristal acetate (Esmya®)  
J-867 (Asoprisnil)  
ZK98299 (Onapristone)  
Telapristone acetate (Proellex®)

Spitz IM. Curr Opin Investig Drugs 2006;7:882–90  

SPRM: Selective Progesterone Receptor Modulator  
UPA: Ulipristal acetate
SPRM MODE OF ACTION:
EFFECT ON PITUITARY AND ENDOMETRIUM

Ulipristal Acetate (UPA) - ESMYA:
- Inhibits ovulation (progesterone levels maintained low)
- Reduces LH and FSH secretion while maintaining mid follicular estrogen levels
- Direct effect on the endometrium:
  - Fast reduction of bleedings
  - PAEC (~60% of patients, benign, reversible)
  - Endometrial thickness (~10-15% of patients, reversible)
- Direct effect on fibroids, reducing fibroid volume
  - Inhibition of cell proliferation
  - Induction of apoptosis

Esmya SmPC

SPRM: Selective Progesterone Receptor Modulator
UPA: Ulipristal acetate
**PEARL I: BASELINE CHARACTERISTICS**

**Baseline Medical Status**

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N=48)</th>
<th>UPA 5 mg (N=95)</th>
<th>UPA 10 mg (N=94)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean PBAC</strong></td>
<td>460 (119–1284)</td>
<td>487 (118–1645)</td>
<td>411 (102–1570)</td>
</tr>
<tr>
<td><strong>Mean Hemoglobin</strong></td>
<td>9.55 g/dL</td>
<td>9.32 g/dL</td>
<td>9.46 g/dL</td>
</tr>
<tr>
<td><strong>Mean hematocrit</strong></td>
<td>32.5%</td>
<td>32.1%</td>
<td>32.4%</td>
</tr>
</tbody>
</table>

**Exclusion Criteria**

- Premenopausal women (aged 18–50 years) with uterine myoma(s)
  - ≥1 uterine myoma of ≥3 cm diameter but no myoma >10 cm diameter
- Excessive uterine bleeding
  - PBAC score >100 during Days 1–8 of menstruation
- Anaemia required (Hg < 10.2 mg/dl)
- Eligible for surgical procedure
  - Hysterectomy, myomectomy, uterine artery embolisation or endometrial ablation

**Design**

- Once-daily oral UPA 5 mg + concomitant iron n=95
- Once-daily oral UPA 10 mg + concomitant iron n=94
- Once-daily oral Placebo + concomitant iron n=48

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**ITT Population**

*ITT Population  
^PBAC: Pictorial Bleeding Assessment Chart

PEARL I:
BLEEDING CONTROL IN MORE THAN 90% OF WOMEN TREATED WITH UPA
(PRIMARY ENDPOINT)

Patients with PBAC <75 at the End Of Treatment (EOT), week 13; ITT

* *p<0.001 vs. placebo

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Week 13</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>18.40%</td>
</tr>
<tr>
<td>UPA 5 mg</td>
<td>91.35%</td>
</tr>
<tr>
<td>UPA 10 mg</td>
<td>92.43%</td>
</tr>
</tbody>
</table>

Bleeding was controlled 7 days from treatment initiation, in
- 75.9% of UPA 5 mg patients and
- 82.7% of patients in the UPA 10 mg group

UPA: Ulipristal acetate

**PEARL II: BASELINE CHARACTERISTICS**

**Inclusion Criteria**

- Premenopausal women (aged 18–50 years) with uterine myoma(s)
  - ≥1 uterine myoma of ≥3 cm diameter but no myoma >10 cm diameter

- Excessive uterine bleeding
  - PBAC score >100 during Days 1–8 of menstruation

- Anaemia not required

- Eligible for surgical procedure
  - Hysterectomy, myomectomy, uterine artery embolisation or endometrial ablation

**Baseline Medical Status**

<table>
<thead>
<tr>
<th>Baseline Medical Status</th>
<th>UPA 5mg (N=93)</th>
<th>UPA 10 mg (N=95)</th>
<th>Lupron 3,75 mg (N=93)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean PBAC</td>
<td>379 (109–1984)</td>
<td>328 (120–1809)</td>
<td>404 (102–2104)</td>
</tr>
</tbody>
</table>

*ITT Population  PBAC: Pictorial Bleeding Assessment Chart

PEARL II:
TIME TO CONTROL OF BLEEDING

PBAC<75

UPA 5 mg
UPA 10 mg
Lupron 3.75 mg

UPA normalised bleeding faster than GnRHa (7 days vs 30 days)

UPA: Ulipristal acetate

PEARL II:
UPA STOPS BLEEDING FASTER AND MORE CONSISTENTLY VS GnRHa (INDIVIDUAL PATIENT DATA)

After first menstruation, most UPA patients are in amenorrhoea, while many GnRHa patients have further bleeds during the next 3 weeks due to flare-up effect.

UPA: Ulipristal acetate

PEARL I (POST HOC ANALYSIS):
INDIVIDUAL BLEEDING EXPERIENCE

OBJECTIVES
● To analyse the Individual Bleeding Pattern of patients treated with UPA for 90 days:
  • During the period from 1\textsuperscript{st} menstruation, at which UPA is started, until the treatment is completed
  • In the presence of sub-mucosal fibroids vs. no fibroids protruding in the uterine cavity
  • In the presence of PAEC vs. no PAEC

METHODOLOGY
● Post-hoc sub-analysis of PEARL I data

UPA: Ulipristal acetate

Data on file. PEARL I Post hoc analysis on menstrual bleeding experience in PEARL I clinical study
PGL4001’s (ulipristal acetate) Efficacy Assessment in Reduction of symptoms due to uterine Leiomyomata
PEARL I:
BLEEDING RESULTS SUMMARY

**Bleeding Control at the EOT:**
- UPA 5 mg PBAC < 75: 91.5%
- UPA 10 mg PBAC <75: 92.3%

**Amenorrhea at EOT:**
- UPA 5 mg PBAC < 2: 73.4%
- UPA 10 mg PBAC<2: 81.3%

EOT: End of Treatment
UPA: Ulipristal acetate

PEARL I (POST HOC ANALYSIS)

What was the individual bleeding pattern of women over the 13 week treatment course?

There are established descriptions of bleeding patterns in the literature that permit classification of experience.

Can these better illuminate the data in terms of individual experience?

Data on file. PEARL I Post hoc analysis on menstrual bleeding experience in PEARL I clinical study PGL4001’s (ulipristal acetate) Efficacy Assessment in Reduction of symptoms due to uterine Leiomyomata
PEARL I (POST HOC ANALYSIS)
NO BLEEDING OR PBAC<12 OVER 90 DAYS

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<tr>
<td>No Bleeding</td>
<td>No bleeding or PBAC &lt;12 over 90 days</td>
<td>2.1%</td>
<td>63.9%</td>
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Adapted from WHO Belsey System of Bleeding Pattern

This system establishes criteria for defining clinically important bleeding patterns during a 90-day reference period.

UPA: Ulipristal acetate

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<td>2.1%</td>
<td>63.9%</td>
</tr>
<tr>
<td>Infrequent Bleeding</td>
<td>1 or 2 bleeding-spotting episodes</td>
<td>6.3%</td>
<td>17.9%</td>
</tr>
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This system establishes criteria for defining clinically important bleeding patterns during a 90-day reference period.

UPA: Ulipristal acetate
PEARL I (POST HOC ANALYSIS)
SUBMUCOUS FIBROIDS AND BLEEDING PATTERNS IN PEARL I

Women with sub-mucous fibroids are more likely to have 1 of the 3 “Other bleeding patterns” (irregular, frequent or prolonged)

UPA: Ulipristal acetate

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PGL4001’s (ulipristal acetate) Efficacy Assessment in Reduction of symptoms due to uterine Leiomyomata
PEARL I (POST HOC ANALYSIS)

What was the experience of individual women over the 13 week treatment phase?

Were women who experienced the “other” bleeding patterns (i.e. Irregular, Prolonged or Frequent Bleeding) more likely to have PAEC?

PAEC: glandular cyst dilatation

PAEC: low mitotic activity
PEARL I (POST HOC ANALYSIS)
INFLUENCE OF PAEC ON BLEEDING PATTERN

Women with PAEC does not seem to influence the ability of UPA to control the bleeding

UPA: Ulipristal acetate

UPA group (n=115)
- Presence of PAEC: 80%
- Non Presence of PAEC: 12.5%

UPA group (n=40)
- Presence of PAEC: 20%
- Non Presence of PAEC: 87.5%

Data on file. PEARL I Post hoc analysis on menstrual bleeding experience in PEARL I clinical study
PGL4001’s (ulipristal acetate) Efficacy Assessment in Reduction of symptoms due to uterine Leiomyomata
CONCLUSIONS ON BLEEDING CONTROL
PEARL I & PEARL II

UPA treatment rapidly stops excessive bleeding
- Bleeding control (defined as PBAC < 75) in > 90% by EOT
- Bleeding control obtained within 10 days of treatment
- Induces amenorrhoea (defined as PBAC < 2) in > 70% by EOT
- Stops heavy bleeding faster than GnRHa

UPA: Ulipristal acetate

CONCLUSIONS PEARL I (POST HOC ANALYSIS)

Bleeding control:

- The predominant bleeding pattern in women treated with UPA is "No bleeding" (defined as "no bleeding" or PBAC < 12 in a 90 days period)
  - 63.9% with UPA 5mg and 71.3% with UPA 10mg

Submucosal fibroids:

- Women with submucosal fibroids are more likely to experience prolonged, irregular and frequent bleeding,
- The vast majority of women with submucosal fibroids experienced no bleeding

PAEC:

- Was not a factor in the bleeding patterns and did not influence the ability of UPA to control bleeding

UPA: Ulipristal acetate