Advances in Leiomyoma Research

2nd NIH International Congress

Feb. 24-25, 2005, Bethesda, MD

Effectiveness of Asoprisnil, a Selective Progesterone Receptor Modulator (SPRM), in Treating Uterine Leiomyomata

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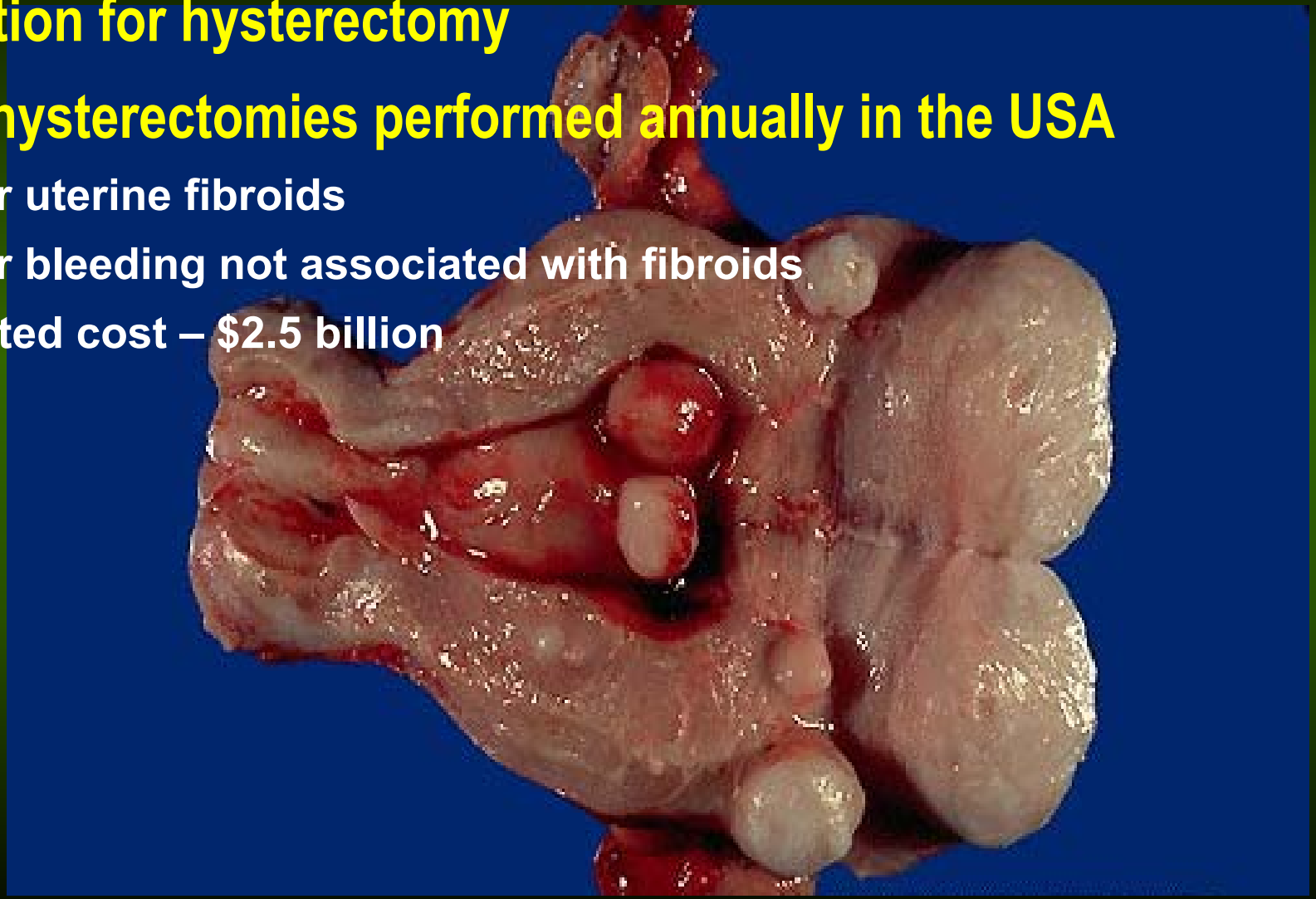
Uterine Fibroids

- Prevalence: 30-40% of women in reproductive age
- Major indication for hysterectomy
  - 650,000 hysterectomies performed annually in the USA
    - 40% for uterine fibroids
    - 20% for bleeding not associated with fibroids
    - Estimated cost – $2.5 billion



SPRMs

- SPRMs are novel PR ligands that exert clinically relevant tissue-selective, and partial (mixed) agonist/antagonist effects in animals and humans
- Asoprisnil (J867) is the first SPRM to reach an advanced stage of clinical development for the treatment of symptomatic leiomyomata and endometriosis
- Asoprisnil manifests both tissue selectivity and PR specificity

Asoprisnil (J867)
Tissue selectivity

- High degree of uterine selectivity
  - Induction of amenorrhea by targeting the endometrial vasculature
  - Selective inhibition of endometrial proliferation
  - Selective antiproliferative effect on uterine leiomyomata
  - No antiproliferative effects on other reproductive tract tissues
  - Follicular phase estradiol concentrations are maintained

- Asoprisnil, unlike antiprogestins (e.g.mifepristone):
  - Does not effectively terminate pregnancy in relevant animal models of human parturition

- Asoprisnil, unlike progestins:
  - Des not induce breakthrough bleeding
  - Produces substantially less premenstrual syndrome-like effects
  - Has the potential to inhibit breast proliferation

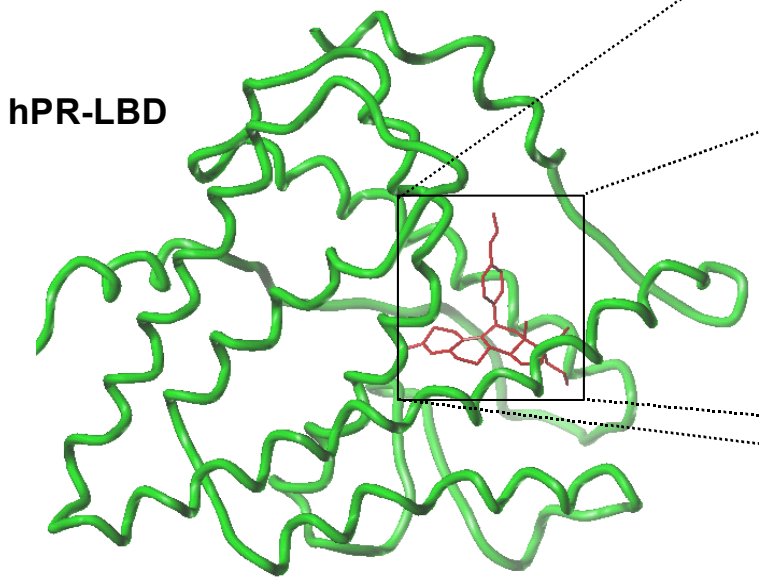
Asoprisnil (J867)
Receptor specificity

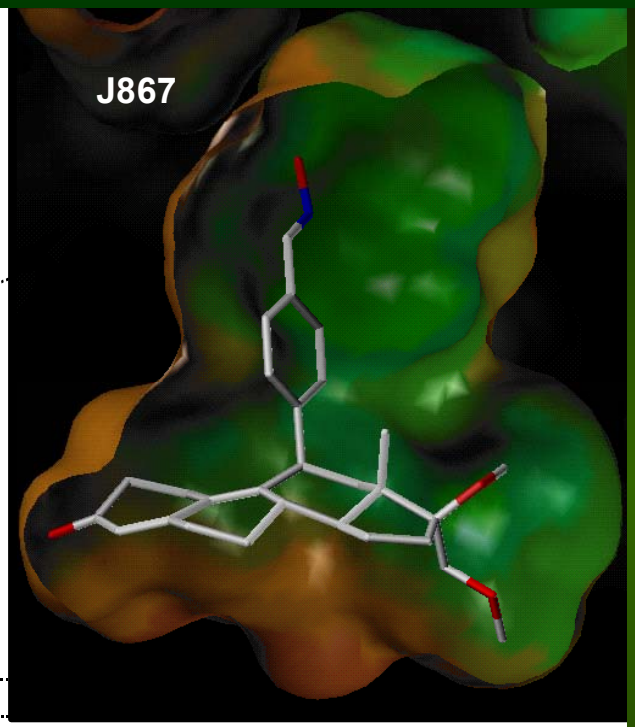
- **PR: High binding affinity (3x greater than progesterone)**
- **GR: Moderate binding affinity**
  - **No antiglucocorticoid effects in humans**
- **AR: Low binding affinity**
  - Mixed agonist/antagonist at AR in animal models
  - No androgenic side-effects in humans
- **ER: No receptor binding**

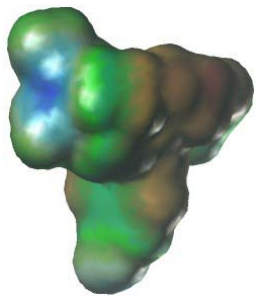
(DeManno et al. Steroids 2003; 68,1019-1032)

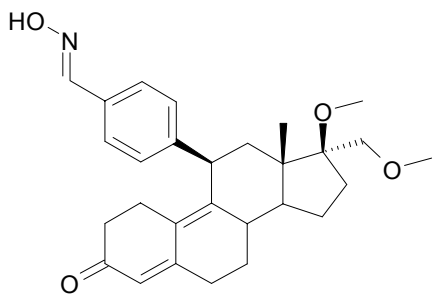
Asoprisnil (J867)

(WHO, USAN)

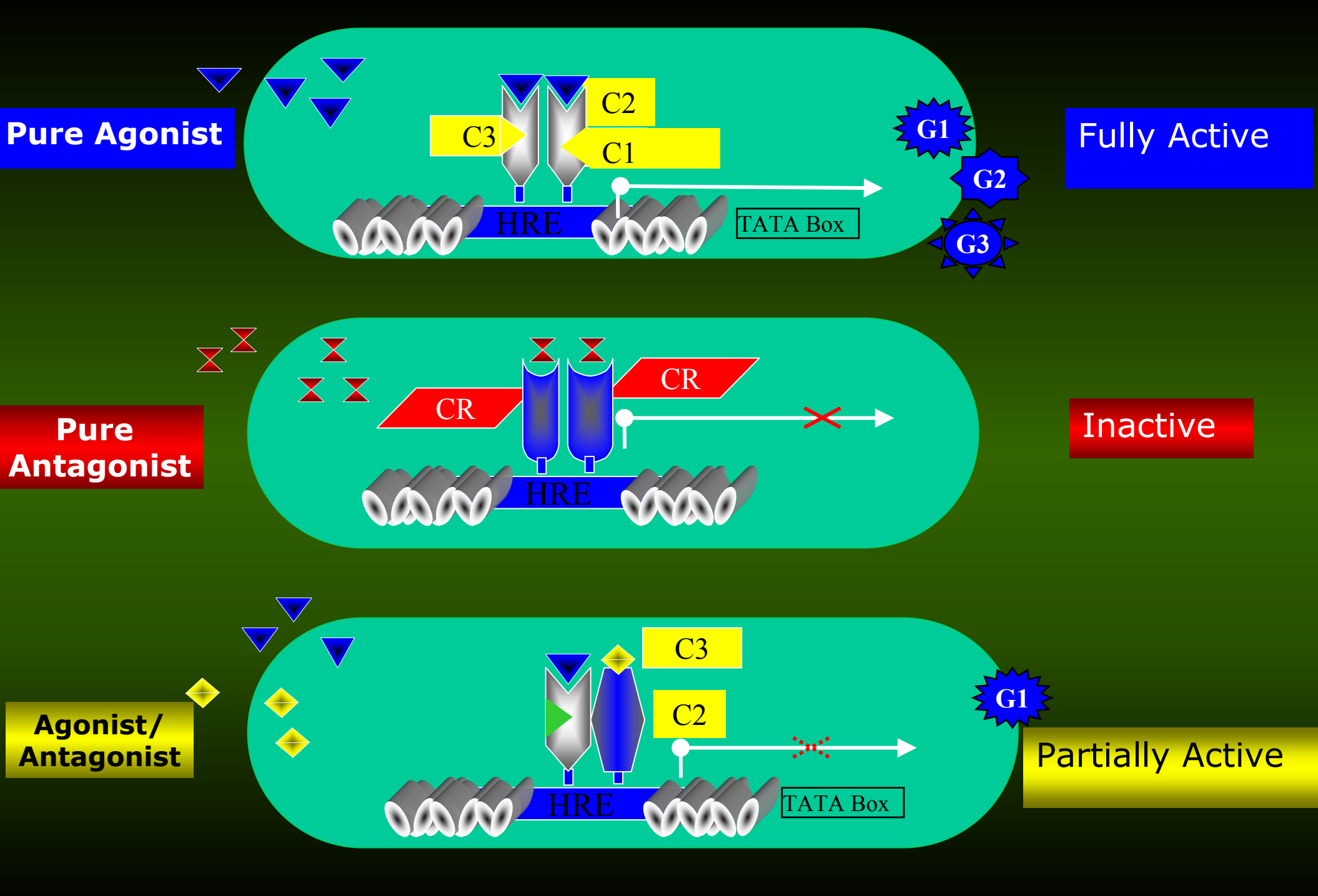




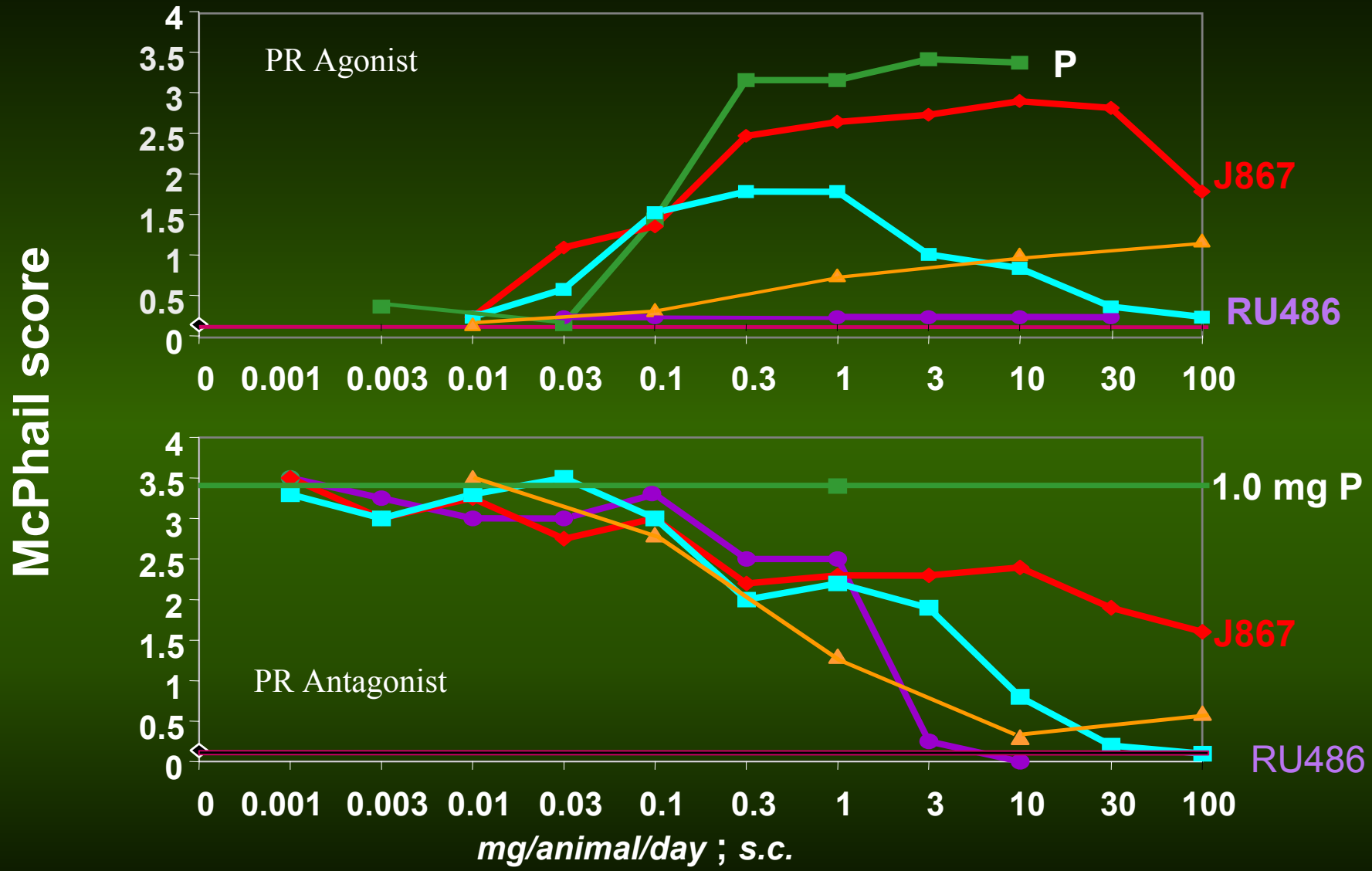




(Benzaldehyde, 4-[(11ß, 17ß)-17-methoxy-17- (methoxy-methyl) -3-oxoestra-4, 9-dien-11-yl]-1-(E)-oxime)

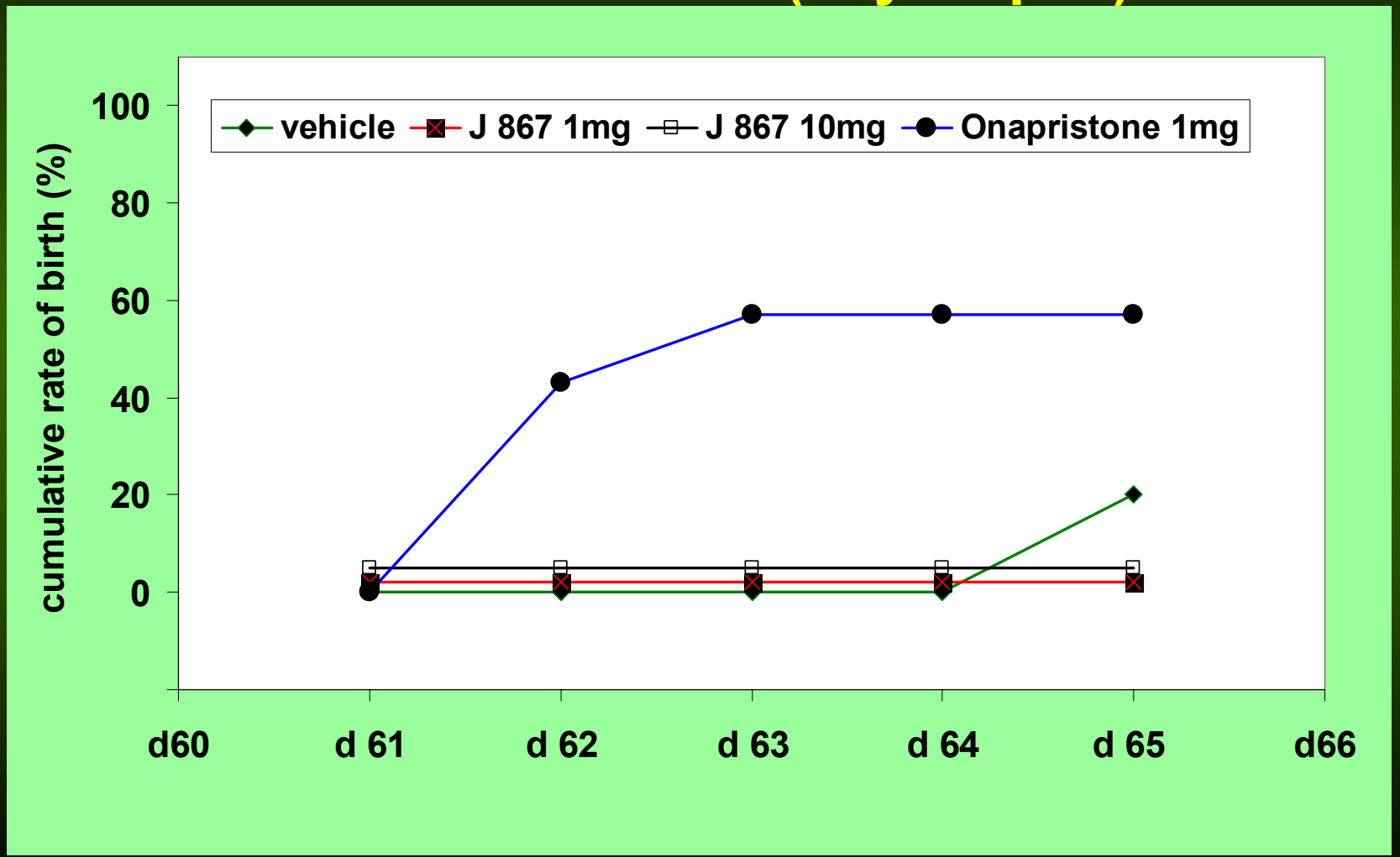

Pure Agonist
C2
C3
C1
G1
G2
G3
HRE
TATA Box
Fully Active
Pure Antagonist
CR
CR
HRE
Inactive
Agonist/ Antagonist
C3
C2
G1
HRE
TATA Box
Partially Active

PR agonist and antagonist activities of SPRMs in the rabbit uterus



Effects of the SPRM asoprisnil (1mg, 10 mg) compared to the pure PR antagonist onapristone (1 mg), and vehicle control in guinea pigs during late pregnancy

- s.c. treatments (day 60 p.c.)



(DeManno et al. Steroids 2003; 68,1019-1032)

Asoprisnil Phase II Uterine Leiomyoma Study (M99-144)

Study Objectives

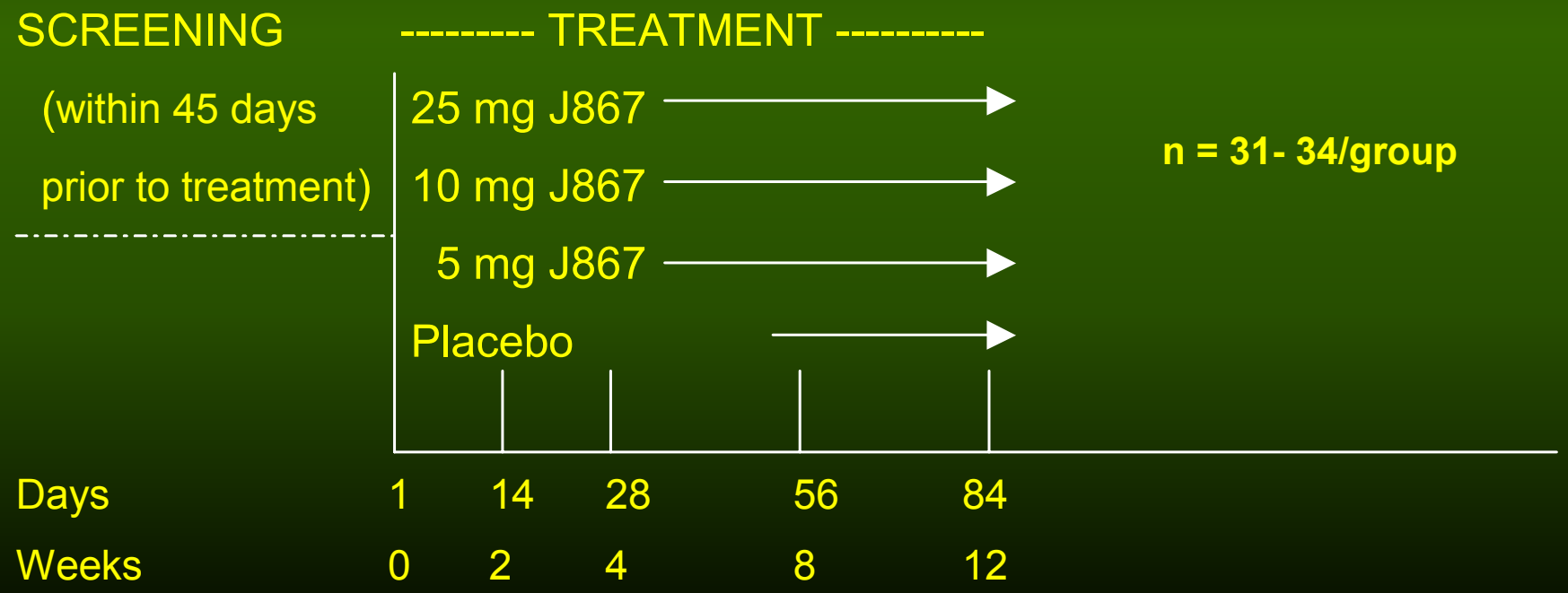
- To determine safety and efficacy of 3 doses of asoprisnil in comparison with placebo in subjects with uterine leiomyomas

(Chwalisz at al., J Soc Gynecol Invest 2003;10)

Asoprisnil Phase II Uterine Leiomyoma Study (M99-144)

Design

- A multicenter, randomized, placebo-controlled, double-blind, parallel-group study of asoprisnil (5, 10, and 25 mg) administered orally once daily for 12 weeks



(Chwalisz at al., J Soc Gynecol Invest 2003;10)

Asoprisnil Phase II Uterine Leiomyoma Study (M99-144)

Endpoints

Efficacy

- Uterine Fibroid Size
  - % change from baseline in uterine volume and volume of the largest fibroid measured by ultrasonography
- Bleeding pattern
- Uterine Leiomyoma Symptom Assessment Score
- Hematologic parameters
- Global efficacy question

Safety

- Endometrial biopsy (screening, week 12)
- Laboratory parameters & hormones
- Adverse events

(Chwalisz at al., J Soc Gynecol Invest 2003;10)

Asoprisnil Phase II Uterine Leiomyoma Study (M99-144)

Assessment of uterine bleeding

- Daily bleeding diary
  - 0 = none;
  - 1 = spotting; light bleeding, no sanitary protection needed
  - 2 = light; 1-2 regular tampons or pads/24 hours
  - 3 = medium; 3-4 regular tampons or pads/24 hours
  - 4 = heavy; > 4 tampons or pads/24 hours
- Monthly menorrhagia score
  - 0 = normal flow, no floods or clots (FC)
  - 1 = mild; bleeding ≤ 5 days with FC
  - 2 = moderate; bleeding 6-8 days with FC
  - 3 = severe; bleeding > 8 days with FC

  } **menorrhagia**
- Hemoglobin concentrations

(Chwalisz at al., J Soc Gynecol Invest 2003;10)

Asoprisnil Phase II Uterine Leiomyoma Study (M99-144)

Key Inclusion Criteria

- Premenopausal subjects (age: 18-49 years)
- Diagnosis of uterine fibroid via ultrasound
  - Fibroid $\geq$ 3.0 cm in diameter or
  - Uterine volume 2x normal size (>200 cm^3) due to multiple small fibroids
- Regular menstrual cycles (21-35 days)
- Negative pregnancy test at screening and Day -1

(Chwalisz at al., J Soc Gynecol Invest 2003;10)

Effects on the Volume of the Dominant Leiomyoma

- Asoprisnil reduced the uterine volume and the volume of the largest leiomyoma in a dose-dependent manner.
- In the 25 mg group, the median percent decrease from baseline in largest leiomyoma volume was statistically significant vs placebo at 4 weeks (16.1%, $p \leq 0.01$) and 8 weeks (26.5%, $p \leq 0.01$) post dosing, and the decrease at 12 weeks was 36.1%.

(Chwalisz at al., J Soc Gynecol Invest 2003;10)

Effects on Pressure Symptoms

- At doses of 10 mg and 25 mg, there was significant reduction in pressure symptoms compared to placebo by week 12
  - Bloating ($p \leq 0.01$ for 10 and 25 mg)
  - Pelvic pressure ($p \leq 0.01$ for 25 mg).

(Chwalisz at al., J Soc Gynecol Invest 2003;10)

Induction of Amenorrhea and Effects on Hemoglobin

- Asoprisnil dose-dependently induced amenorrhea during the entire treatment period
  - placebo: 0%
  - 5 mg: 28.1%
  - 10 mg: 64.3%
  - 25 mg: 83.3%

- A significant increase in hemoglobin concentrations by week 12 was observed in all asoprisnil groups compared to placebo ($p \leq 0.05$ all doses)

(Chwalisz at al., J Soc Gynecol Invest 2003;10)

Effects on Bleeding Patterns

- Daily bleeding diaries showed a dramatic ($p<0.001$), dose-dependent suppression of bleeding reflected in a significant reduction in average monthly spotting and bleeding scores
  - Placebo: 15.6
  - Asoprisnil 5 mg: 7.3
  - Asoprisnil 10 mg: 4.7
  - Asoprisnil 25 mg: 1.3

(Chwalisz at al., J Soc Gynecol Invest 2004;11)

Effects on Menorrhagia Scores

- Subjects with menorrhagia at baseline (76%) showed a dose-dependent decrease in menorrhagia scores after only one month of treatment
- In most of these subjects flow decreased to normal or amenorrhea by month 3
  - Placebo: 24%
  - 5 mg: 78%;
  - 10 mg: 88%
  - 25 mg: 100%

(Chwalisz at al., J Soc Gynecol Invest 2004;11)

Safety Conclusions

- Overall the treatment was well tolerated
  - Headache and abdominal pain were the most frequent adverse events and were equally distributed in all treatment groups

(Chwalisz at al., J Soc Gynecol Invest 2003;10)

Summary and Conclusions

1. Asoprisnil, at doses of 10 mg and 25 mg, was effective in:
   - Shrinking the uterine fibroids,
   - Reducing the intensity and duration of uterine bleeding,
   - Controlling abnormal uterine bleeding (menorrhagia), and
   - Improving mass effect symptoms, such as pelvic pressure and bloating.

   - Asoprisnil has the potential to reduce the number of surgeries for symptomatic uterine fibroids.

(Chwalisz at al., J Soc Gynecol Invest 2003;10)