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

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Uterine leiomyomata are the most common solid pelvic tumors, as well as the most frequently reported indication for surgery in women. Abnormal uterine bleeding (menorrhagia and metrorrhagia) and pressure-related symptoms (pelvic pressure, bloating, etc.) represent the major complaints in women who seek treatment for leiomyomata, and are the major indications for surgical intervention. Recent evidence from biochemical, pharmacological and clinical studies indicate that progesterone and the progesterone receptor (PR) play a key role in the development and regulation of the growth of uterine leiomyomata.

SPRMs represent a new class of PR ligands that exert clinically relevant tissue-selective, and partial **(**mixed) agonist/antagonist effects in animals and humans (1). Asoprisnil (J867), which belongs to the class of 11β-benzaldoxime-substituted estratrienes, is the first SPRM to reach an advanced stage of clinical development for the treatment of women with symptomatic uterine leiomyomata and endometriosis. In primates, asoprisnil shows uterine selective effects in the presence of follicular phase estrogen concentrations (2). It suppresses both endometrial proliferation and bleeding. Asoprisnil exhibits high PR specificity in *in vitro* models, and has no antiglucocorticoid activity in humans when administered at therapeutic doses. Unlike progesterone antagonists, asoprisnil does not induce labor in relevant models of pregnancy and parturition (2). In a Phase I study in healthy premenopausal women, asoprisnil reversibly suppressed menstruation at doses $\geq$ 10 mg QD, irrespective of the effect on luteal phase serum progesterone concentrations, indicative of luteinization (3). The results of this study suggest that asoprisnil induces amenorrhea primarily by targeting the endometrium.

A Phase II multicenter, double blind, placebo-controlled study was conducted to evaluate the effectiveness and safety of asoprisnil in the management of subjects with uterine leiomyomata (4, 5). Asoprisnil 5 mg, 10 mg, 25 mg, or placebo was administered orally once daily for 12 weeks. The treatment was initiated during the first four days of the menstrual cycle. The volume of the largest leiomyoma and the uterus was measured sonographically at baseline and after 4, 8 and 12 weeks of dosing. Uterine bleeding was assessed using a daily bleeding diary (0=none, 1=spotting, 2=light, 3=medium, 4=heavy), a 4-point monthly menorrhagia score, and indirectly by effects on hemoglobin concentrations. Other symptoms of uterine leiomyomata were assessed monthly according to a patient-reported fibroid symptom assessment questionnaire (FSAQ) developed by TAP. Asoprisnil consistently reduced the duration and intensity of uterine bleeding in a dose-dependent manner with the absence of unscheduled bleeding. Asoprisnil treatment also dose-dependently induced amenorrhea throughout the study (placebo 0%; 5 mg 28%, 10 mg 64%, 25 mg 83%), and significantly reduced menorrhagia scores. In subjects with menorrhagia at baseline (76%), there was a dose-dependent decrease in menorrhagia scores after only one month of treatment. In most subjects, flow decreased to normal or amenorrhea by month 3 (5 mg 78%; 10 mg 88%; 25 mg 100% compared to placebo 24%). A significant increase in hemoglobin concentrations by week 12 was observed in all asoprisnil groups compared to placebo ($p \leq 0.05$ all

doses). Asoprisnil reduced the uterine volume and the volume of the largest leiomyoma in a dose-dependent manner, with the maximum decrease of 36% in the 25 mg group at week 12. At doses of 10 mg and 25 mg, there was significant reduction in mass effect symptoms compared to placebo by week 12 (bloating, $p \leq 0.01$ for 10 mg and 25 mg; pelvic pressure, $p \leq 0.01$ for 25 mg). Asoprisnil treatment was well tolerated. The adverse events were evenly distributed among all groups. The most frequently reported adverse events were headache and abdominal pain. There was no significant change in serum estradiol and cortisol concentrations in asoprisnil groups compared to placebo. The most common diagnosis for endometrial biopsies from asoprisnil-treated subjects at week 12 showed non-physiologic secretory effects consistent with weak secretory activity in endometrial glands, absent or rare mitotic activity, variable effects on the endometrial stroma, and the presence of unusual, thick-walled arterioles. These effects were accompanied by a reduction in proliferative patterns.

In summary, the data from early clinical studies with asoprisnil (Phase I and II) demonstrated a favorable safety and tolerability profile. Long-term safety will be established in large, Phase III studies, which are ongoing. Approximately 1000 subjects with menorrhagia associated with uterine leiomyomata, eligible for hysterectomy, were enrolled in these studies. Menstrual pictogram diaries, MRI images, and various quality of life questionnaires are being used to assess the effects of asoprisnil on uterine bleeding, leiomyoma size and symptoms, respectively.

References

1. **Chwalisz K, DeManno D, Garg R, Larsen L, Mattia-Goldberg C, Stickler T** 2004 Therapeutic potential for the selective progesterone receptor modulator asoprisnil in the treatment of leiomyomata. Semin Reprod Med 22:113-9
2. **DeManno D, Elger W, Garg R, et al.** 2003 Asoprisnil (J867): a selective progesterone receptor modulator for gynecological therapy. Steroids 68:1019-32
3. **Chwalisz K, Elger W, Stickler T, Mattia-Goldberg C, Larsen L** 2005 The effects of one-month administration of asoprisnil (J867), a selective progesterone receptor modulator, in healthy premenopausal women. Human Reprod (in press)
4. **Chwalisz K, Lamar Parker R, Williamson S, Larsen L, McCrary K, Elger W** 2003 Treatment of uterine leiomyomas with the novel selective progesterone receptor modulator (SPRM). J. Soc. Gynecol. Invest. 10 (Supplement):Abstract 636
5. **Chwalisz K, Larsen L, McCrary K, Edmonds A** 2004 Effects of the novel selective progesterone receptor modulator (SPRM) asoprisnil on bleeding patterns in subjects with leiomyomata. J Soc Gynecol Invest 11 (Supplement):Abstract 728