The most common benign uterine tumors in reproductive women are uterine leiomyomas or fibroids. Fibroids can cause heavy bleeding, anemia, pelvic pain, dysmenorrheal and infertility. Medical therapy for fibroids is limited and most patients are treated surgically. Oral progestins have been extensively researched but a potential concern when progestins are used is the possibility of promotion of myoma growth. Gonadotropin releasing hormone (GnRH) agonists have proven to be the most effective medical therapy for uterine fibroids. In a placebo-controlled trial, the GnRH agonist leuprolide acetate stopped vaginal bleeding in 85% of the patients with anemia prior to surgery for fibroids. Leuprolide acetate however suppresses estradiol levels dramatically, in the trial by Stovall, et al, 67% of patients reported hot flashes.

Small uncontrolled trials suggest that selective progesterone-receptor modulators (SPRMs) may help control bleedings and shrink fibroids. Ulipristal acetate is an effective and selective modulator of progesterone receptor activity in vitro and in vivo. Studies of cultures leiomyoma cells have shown antiproliferative. Antifibrotic and proapoptotic effects of ulipristal acetate on leiomyoma cells but not on normal myometrial cells.

The effectiveness and the resulting side effects of ulipristal acetate compared with leuprolide acetate have not been defined. This study randomly assigned patients to 3 months of daily therapy with 5mg oral ulipristal acetate, 10mg of daily ulipristal, or 3 monthly 3.75mg intramuscular injections of leuprolide acetate. The study enlisted premenopausal women aged 18 to 50 with a BMI between 18 and 40 who had heavy fibroid bleeding, at least one myoma measuring >3 cm in diameter but not fibroid >10 cm and a uterus no more than 16 weeks size.

The study assessed uterine bleeding using the pictorial blood loss assessment chart (PBAC), a self administered assessment which objectively estimates menstrual blood loss. The PBAC score ranges from 0 to over 500, with higher scores indicating more severe bleeding. For this study menorrhagia was defined as a PBAC score >100 during the first 8 days of the woman’s period. A PBAC score >100 was an eligibility requirement for the trial. Treatment was started within 4 days after the start of the woman’s menstrual period and continued until week 13. Upon completion of therapy all patients were eligible for surgery, which approximately half the subjects chose to pursue. The most common surgical procedure performed in all three groups after study completion was myomectomy.

Demographic and baseline characteristics were balanced among the three study groups with no significant differences among them. The study evaluated all send points at week 13, prior to any surgical procedures. The primary efficacy end point was control of uterine bleeding at week 13, defined as a PBAC score <75. The primary safety objective was demonstration of a superior side-effect profile of ulipristal over leuprolide in terms of estradiol levels at week 13 and the proportion of subjects with moderate to severe hot flashes during therapy.
The results of the study showed that its subjects treated per protocol, a 10mg daily dose of ulipristal acetate was superior to leuprolide acetate with respect to control of bleeding at week 13. A PBAC score <75 was achieved by 84/93 subjects takings 5mg of ulipristal, 82/92 subjects who took leuprolide acetate and in 93/95 subjects taking 10mg ulipristal. The median PBAC score at week 13 was the same for all treatment groups (zero, indicating that most were amenorrheic), but excessive bleeding was controlled and inducement of amenorrhea occurred more rapidly in patients receiving either 5mg or 10mg of ulipristal acetate.

Among women in the ulipristal groups, menstruation returned on average 31 to 34 days after the end of treatment. For the leuprolide group, menstruation returned approximately 43 days after the treatment was concluded. With respect to effects on bone, at week 13 the median level of type 1 CTX (a marker of bone resorption) was significantly greater for the leuprolide group than for either of the ulipristal groups. At week 13 median estradiol values were 64 pg/ml in the group taking 5mg ulipristal, 60.5p/ml in the group taking 10mg ulipristal and 25pg/ml (ie post-menopausal levels) in the leuprolide acetate group. Hot flashes were reported in 10% of women taking either dose of ulipristal but in 40% of those using leuprolide.

At 13 weeks medium volume reduction of the three largest fibroids on each subject was 36%, 42%, and 53% in the 5mg ulipristal, 10 mg ulipristal and leuprolide acetate groups respectively. The leuprolide acetate group thus had the largest median reduction in fibroid volume. Similarly, total uterine volume was decreased by about 20% in both ulipristal groups, but by 47% in the leuprolide acetate group. In the subpopulation of patients who did not subsequently undergo surgery, fibroids began to enlarge approximately 1 month after the last dose of leuprolide acetate, while reduction of fibroid volume in the ulipristal groups appeared to be sustained for at least 6 months after conclusion of treatment. Endometrial biopsy at week 13 demonstrated benign endometrium without features of concern in all patients, with exception of one patient with simple hyperplasia who received 5 mg of ulipristal acetate.

Oral ulipristal acetate at 5mg or 10mg was not inferior to leuprolide acetate in controlling bleeding symptoms in women with fibroids. Based on the efficacy outcome selected, the 10 mg dose actually provided statistically superior control of bleeding. Both the doses of ulipristal achieved these results with significantly less suppression of estradiol levels and fewer hot flashes reported by users.