ORIGINAL ARTICLE

Ulipristal Acetate versus Leuprolide Acetate for Uterine Fibroids

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ABSTRACT

BACKGROUND

The efficacy and side-effect profile of ulipristal acetate as compared with those of leuprolide acetate for the treatment of symptomatic uterine fibroids before surgery are unclear.

METHODS

In this double-blind noninferiority trial, we randomly assigned 307 patients with symptomatic fibroids and excessive uterine bleeding to receive 3 months of daily therapy with oral ulipristal acetate (at a dose of either 5 mg or 10 mg) or once-monthly intramuscular injections of leuprolide acetate (at a dose of 3.75 mg). The primary outcome was the proportion of patients with controlled bleeding at week 13, with a prespecified noninferiority margin of –20%.

RESULTS

Uterine bleeding was controlled in 90% of patients receiving 5 mg of ulipristal acetate, in 98% of those receiving 10 mg of ulipristal acetate, and in 89% of those receiving leuprolide acetate, for differences (as compared with leuprolide acetate) of 1.2 percentage points (95% confidence interval [CI], –9.3 to 11.8) for 5 mg of ulipristal acetate and 8.8 percentage points (95% CI, 0.4 to 18.3) for 10 mg of ulipristal acetate. Median times to amenorrhea were 7 days for patients receiving 5 mg of ulipristal acetate, 5 days for those receiving 10 mg of ulipristal acetate, and 21 days for those receiving leuprolide acetate. Moderate-to-severe hot flashes were reported for 11% of patients receiving 5 mg of ulipristal acetate, for 10% of those receiving 10 mg of ulipristal acetate, and for 40% of those receiving leuprolide acetate (P<0.001 for each dose of ulipristal acetate vs. leuprolide acetate).

CONCLUSIONS

Both the 5-mg and 10-mg daily doses of ulipristal acetate were noninferior to once-monthly leuprolide acetate in controlling uterine bleeding and were significantly less likely to cause hot flashes. (Funded by PregLem; ClinicalTrials.gov number, NCT00740831.)

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N Engl J Med 2012;366:421-32.

Uterine leiomyomas, or fibroids, are the most common benign uterine tumors in women of reproductive age. In addition to anemia caused by heavy bleeding, fibroids can cause pelvic pain, pressure, dysmenorrhea, reduced quality of life, and infertility. Current management strategies consist mainly of surgical or radiologic interventions; options for medical therapy are limited.[1-4] The use of oral progestin has not been extensively investigated, but small studies report breakthrough bleeding[5] and possible promotion of myoma growth.[6] The use of a progestin-releasing intrauterine device controls menorrhagia in some patients, but trials have generally excluded patients with uteri distorted by submucosal myomas.[7] Gonadotropin-releasing hormone (GnRH) agonists are considered to be the most effective medical therapy.[8,9] In a placebo-controlled trial, the GnRH agonist leuprolide acetate (in a 3.75-mg depot formulation) stopped vaginal bleeding in 85% of patients with anemia before myoma surgery. However, leuprolide acetate suppresses estradiol, and in that trial, 67% of patients reported hot flashes.[10]

Small pilot studies and other uncontrolled trials of mifepristone[11] and selective progesterone-receptor modulators (SPRMs) have suggested that these agents may be useful in treating fibroids.[12,13] Ulipristal acetate is a potent and selective modulator of progesterone-receptor activity in vitro and in vivo.[13-15] Studies of cultured leiomyoma cells have shown antiproliferative, antifibrotic, and proapoptotic effects of ulipristal acetate on leiomyoma cells but not on normal myometrial cells.[16] In addition, SPRMs have pharmacodynamic effects on the endometrium, including antiproliferative effects that may contribute to the induction of amenorrhea.[12,17-19] In small placebo-controlled trials,[20,21] ulipristal acetate reduced fibroid and uterine sizes in women with symptomatic fibroids.

In this study, the PGL4001 (Ulipristal Acetate) Efficacy Assessment in Reduction of Symptoms Due to Uterine Leiomyomata (PEARL II) trial, we evaluated whether daily oral ulipristal acetate (5 mg or 10 mg) was noninferior to a monthly intramuscular injection of leuprolide acetate (3.75 mg) in controlling bleeding before planned surgery for symptomatic fibroids and compared the side-effect profiles of the two drugs.

Methods

Study Design

PEARL II was a randomized, parallel-group, double-blind, double-dummy, active-comparator–controlled, phase 3 trial to assess the efficacy and safety of ulipristal acetate, as compared with leuprolide acetate, in the preoperative treatment of symptomatic fibroids. The study was approved by the independent ethics committee at each study site and was conducted in accordance with the principles of the International Conference on Harmonization–Good Clinical Practice (ICH-GCP) guidelines. The original protocol, amendments, and statistical analysis plan are available with the full text of this article at NEJM.org.

Study Population

We enrolled premenopausal women between the ages of 18 and 50 years who had a body-mass index (the weight in kilograms divided by the square of the height in meters) of 18 to 40, heavy uterine bleeding caused by fibroids, at least one myoma measuring 3 cm or more in diameter (but no myoma measuring >10 cm), and a uterine size equivalent to that of a pregnancy of no more than 16 weeks of gestation; all patients were eligible for surgery. The main exclusion criteria are listed in Table 1 in the Supplementary Appendix, available at NEJM.org. All patients provided written informed consent.

Assessment of Uterine Bleeding

We assessed uterine bleeding using the pictorial blood-loss assessment chart (PBAC),[22,23] an instrument that objectively estimates menstrual-blood loss. The PBAC scale ranges from 0 to more than 500 (with no defined upper limit), with higher scores indicating a greater severity of bleeding. At screening, patients were provided with standardized sanitary materials and were instructed to record the number of tampons or pads used and the extent of soiling with blood (see the Methods section in the Supplementary Appendix for more details). Patients were asked to complete the PBAC daily throughout the treatment period to week 13 and for 28 days preceding the no-treatment follow-up visits at weeks 26 and 38. The PBAC score for a 4-week period was calculated from the sum of daily PBAC results for 28 days. Menorrhagia was defined as a PBAC score of more

than 100 (during the first 8 days of menstruation), which corresponds to blood loss of more than 80 ml. A PBAC score of more than 100 was an eligibility criterion.

RANDOMIZATION AND TREATMENT

Patients were randomly assigned in a 1:1:1 ratio to receive either 5 mg or 10 mg of daily oral ulipristal acetate plus an intramuscular saline injection once monthly or a daily oral placebo plus an intramuscular injection of 3.75 mg of leuprolide acetate once monthly (Fig. 1). The randomization list followed a stratification process for avoiding imbalance with respect to race or ethnic group among the three study groups. A Web-integrated voice-response system transmitted the randomization to the packaging organization, which delivered the medications to the treatment centers. Treatment was started within 4 days after the start of the menstrual period and was continued until week 13, after which patients could have surgery. Follow-up visits were scheduled, without further treatment, for weeks 17, 26, and 38. Iron supplementation was left to the discretion of the treating physician.

END POINTS

We evaluated all efficacy end points at week 13 before surgery. The primary efficacy end point was the proportion of patients with control of uterine bleeding at week 13, which was defined as a PBAC score (summed over the preceding 28-day period) of less than 75 (i.e., in the normal range).[22,23] The prespecified noninferiority margin of –20% was based on clinical judgment.

Secondary efficacy end points included bleeding pattern (consecutive 28-day PBAC scores), amenorrhea (28-day PBAC score, ≤2), changes from baseline in fibroid and uterine volume (on the basis of ultrasonography, performed at each center), global pain score (on the Short-Form McGill Pain Questionnaire[24] and visual-analogue scale), and the Uterine Fibroid Symptom and Quality of Life questionnaire[25] (consisting of a symptom-severity score and a health-related quality-of-life score). (For scoring details, see the Study Design section in the Supplementary Appendix.) Hemoglobin levels, hematocrit, and ferritin levels were measured at all visits. Efficacy end points were assessed every 4 weeks except for the uterine fibroid symptoms and fibroid and uterine volume, which were assessed at baseline and at week 13. Efficacy end points beyond week 13 were exploratory.

The coprimary safety objectives were to show a superior side-effect profile for ulipristal acetate versus leuprolide acetate in terms of serum estradiol levels at week 13 and the proportion of patients with moderate-to-severe hot flashes during treatment. The frequency and severity of adverse events (as spontaneously reported by patients or elicited by nonleading questions) were recorded on standard forms at every visit up to week 17. Serious adverse events were recorded up to week 38. Adverse events occurring more than 4 weeks after the end of treatment were recorded if they were deemed to be related to a study drug or involved uterine hemorrhage.

Secondary safety end points included hematologic and other laboratory assessments, including bone-turnover markers (urinary N-terminal propeptide of type I procollagen [P1NP], type I collagen C-telopeptide [CTX], and bone-specific alkaline phosphatase [BSAP] and deoxypyridinoline [DPD]). Levels of serum estradiol, progesterone, corticotropin, thyrotropin, and prolactin were recorded at baseline and at weeks 5, 9, 13, and 17. The results of hematologic and biochemical analyses, including testing of lipids and glucose, were recorded at all visits up to week 38.

Endometrial thickness and ovaries were assessed at each center by means of ultrasonography at baseline and at weeks 13, 17, 26, and 38. Endometrial biopsy samples (which were obtained before inclusion and at weeks 13 and 38 unless hysterectomy or endometrial ablation was performed) were assessed by three independent pathologists who were unaware of study-group assignments, the visit sequence, and one another's assessments. In view of previous reports of endometrial changes associated with SPRMs, as described by Mutter et al.,[17] standard diagnostic criteria[18] and terminology for endometrial changes associated with SPRMs were used.

STUDY OVERSIGHT

The study was designed by PregLem with the involvement of academic investigators and a trial statistician. Ulipristal acetate was supplied by PregLem, and leuprolide acetate (Enanthone) was purchased from Takeda Pharmaceuticals. Data were collected by an independent contract research organization (ICON Clinical Research) and han-

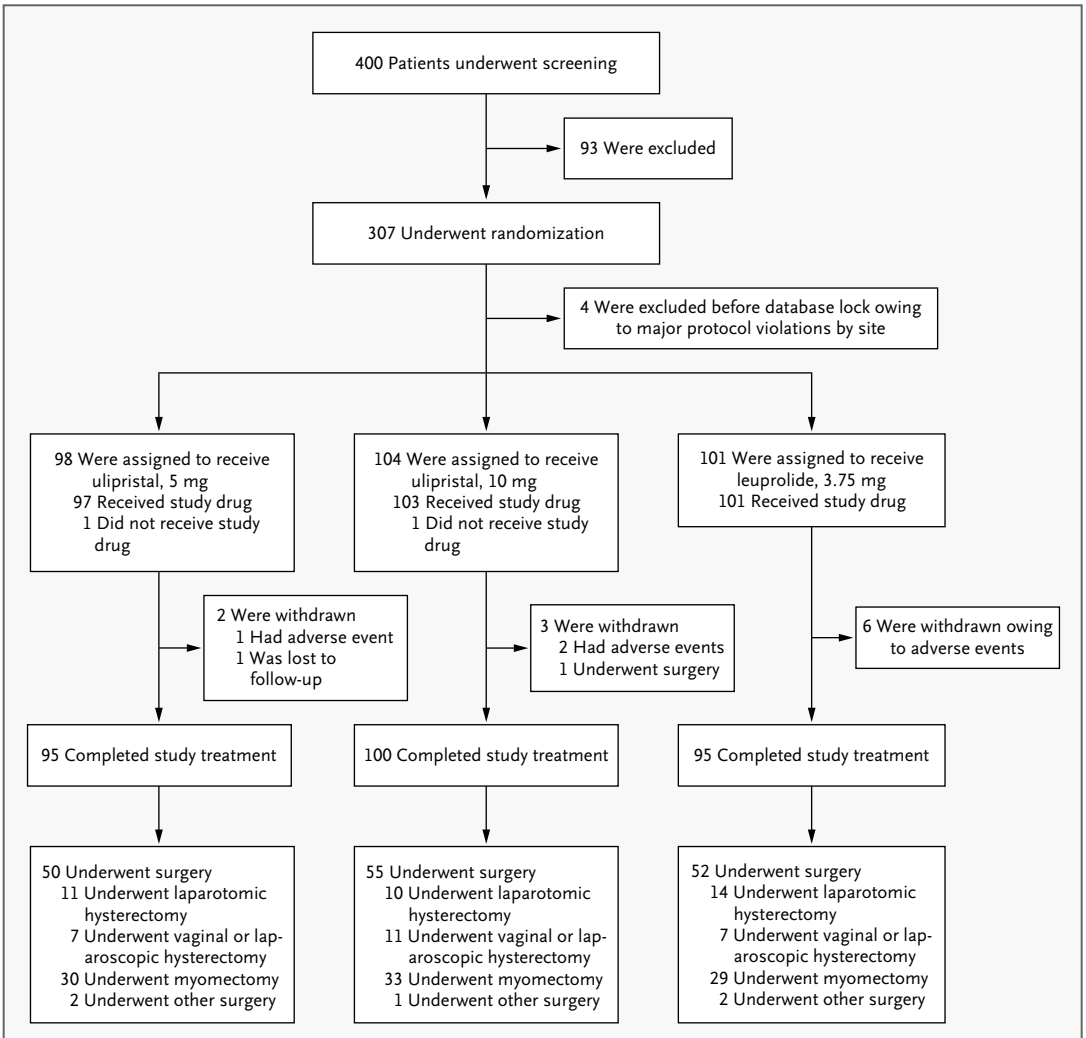

Figure 1. Enrollment and Outcomes.

One patient who was assigned to receive 5 mg of ulipristal acetate actually received 10 mg of the drug. This patient was included in the 10-mg group for the safety analyses and in the 5-mg group for the intention-to-treat efficacy analyses and was excluded from the per-protocol analyses. Three patients (one who was assigned to receive 10 mg of ulipristal acetate and two who were assigned to the leuprolide group) were excluded from the modified intention-to-treat population because of missing efficacy data. These three patients are included in the number who withdrew from treatment. Data for the primary end-point assessment at week 13 were collected before patients underwent surgery.

dled and analyzed by an independent data-management organization (MDSL International). The first and subsequent drafts of the manuscript were prepared by the first author with editorial assistance of the sponsor. All the authors made the decision to submit the manuscript for publication. The first author vouches for the accuracy of the data and analyses and the fidelity of the study to the protocol.

STATISTICAL ANALYSIS

We based the sample size on the requirement to show the noninferiority of ulipristal acetate versus leuprolide acetate with a power of 90%, using a prespecified noninferiority margin of –20%. Allowing for a 15% rate of dropout or protocol violations, we determined that we needed to enroll 285 patients (95 per study group), assuming response rates of 85% in each study group.

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Ulipristal Acetate		Leuprolide Acetate
	5-mg Dose	10-mg Dose	
Safety population			
Patients — no.	97	103	101
Age — yr	40.1±6.2	40.7±6.3	40.3±6.2
Race or ethnic group — no. (%)†			
White	83 (86)	88 (85)	85 (84)
Black	9 (9)	11 (11)	9 (9)
Other	5 (5)	4 (4)	7 (7)
Body-mass index‡	25.4±4.1	26.2±4.7	24.9±4.1
Serum estradiol — pg/ml			
Median	40.0	37.0	39.0
Interquartile range	27.5–54.0	28.0–59.0	29.0–57.0
Endometrial thickness — mm	8.9±4.2	8.9±4.3	9.0±3.9
Per-protocol population			
Patients — no.	93	95	93
Score on pictorial blood-loss assessment chart§			
Median	286	271	297
Interquartile range	190–457	183–392	189–443
Total volume of three largest myomas — cm^3			
Median	79.6	47.6	59.2
Interquartile range	30.3–151.0	24.1–110.6	27.8–156.3
Uterine volume — cm^3			
Median	199.4	197.8	199.9
Interquartile range	149.6–315.0	120.9–297.7	138.2–271.9
Hemoglobin — g/dl	12.4±1.6	12.4±1.6	12.1±1.8
Pain assessment — median score (IQR)			
Short-Form McGill Pain Questionnaire¶	9.0 (4.0–17.0)	7.0 (4.0–16.0)	7.0 (3.0–17.5)
Visual-analogue scale‖	49.0 (23.5–59.0)	46.5 (20.0–66.5)	46.0 (21.0–62.0)
Uterine Fibroid Symptom and Quality of Life questionnaire**			
Symptom severity	54.0±20.0	48.9±22.1	52.5±21.7
Health-related quality of life total score	53.3±19.9	56.5±21.4	50.1±24.9

* Plus–minus values are means ±SD. There was no significant difference between ulipristal acetate (either dose) and leuprolide acetate for any baseline variable. IQR denotes interquartile range.
† Race or ethnic group was reported by the site investigator.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.
§ Scores on the pictorial blood-loss assessment chart range from 0 to more than 500, with higher scores indicating greater blood loss.
¶ Scores on the Short-Form McGill Pain Questionnaire range from 0 to 45, with higher scores indicating a greater severity of pain.
‖ Scores on the visual-analogue scale range from 0 to 100, with higher scores indicating a greater severity of pain.
** On the Uterine Fibroid Symptom and Quality of Life questionnaire, scores for symptom severity range from 0 to 100, with higher scores indicating increased severity. Total scores for health-related quality of life range from 0 to 100, with higher scores indicating a better quality of life.

Table 2. Key Efficacy End Points and Safety Outcomes at 13 Weeks for Ulipristal Acetate, as Compared with Leuprolide Acetate.*

Variable	Ulipristal Acetate		Leuprolide Acetate	Difference (Ulipristal Acetate vs. Leuprolide Acetate)	
	5-mg Dose	10-mg Dose		5-mg Dose	10-mg Dose
				percentage points (95% CI)	
Per-protocol population					
No. of patients	93	95	93		
Score on pictorial blood-loss assessment chart					
<75 — no./total no. (%)	84/93 (90)	93/95 (98)	82/92 (89)†	1.2 (–9.3 to 11.8)‡	8.8 (0.4 to 18.3)‡
Median (IQR)	0 (0 to 2)	0 (0 to 0)	0 (0 to 1)		
Change from baseline — median (IQR)	–268 (–412 to –172)	–268 (–387 to –179)	–274 (–430 to –161)	6 (–54 to 63)	3 (–45 to 55)
≤2, indicating amenorrhea — no./total no. (%)	70/93 (75)	85/95 (89)	74/92 (80)	–5.2 (–18.7 to 8.6)	9.0 (–2.8 to 21.0)
Total volume of three largest myomas					
Percent change from baseline — median (IQR)	–36 (–58 to –11)	–42 (–69 to –14)	–53 (–69 to –36)		
Ratio to screening volume — geometric mean	0.66	0.61	0.54	1.23 (0.99 to 1.52)	1.12 (0.91 to 1.38)
Uterine volume					
Percent change from baseline — median (IQR)	–20 (–40 to –3)	–22 (–45 to 0)	–47 (–57 to –35)		
Ratio to screening volume — geometric mean	0.84	0.80	0.57	1.48 (1.25 to 1.74)	1.41 (1.19 to 1.66)
Short-Form McGill Pain Questionnaire score					
Median (IQR)	2.0 (0.0 to 4.0)	1.0 (0.0 to 3.0)	0.0 (0.0 to 4.0)		
Change from baseline — median (IQR)	–5.0 (–11.0 to –2.0)	–6.0 (–14.0 to –1.0)	–5.5 (–14.5 to –2.0)	0.2 (–2.0 to 3.0)	0.0 (–2.0 to 2.8)
Uterine Fibroid Symptom and Quality of Life questionnaire					
Health-related quality of life score	76.4±23.2	81.5±22.1	73.2±23.0		
Change from baseline	23.7±26.9	24.8±24.1	23.2±28.2	2.5 (–7.3 to 12.3)	5.6 (–3.9 to 15.1)
Hemoglobin — g/dl	12.8±1.4	12.9±1.2	12.7±1.6	–0.02 (–0.3 to 0.3)	0.03 (–0.3 to 0.3)

Safety population				
No. of patients	97	103	101	
Serum estradiol — pg/ml				
Median	64.0	60.5	25.0	
Interquartile range	45.0 to 110.0	35.0 to 121.0	10.0 to 36.0	
Geometric mean	78.8	69.7	24.0	
Moderate-to-severe hot flashes — no. (%)	11 (11)	10 (10)	40 (40)	−28.3 (−40.6 to −14.6)§ −29.9 (−42.0 to −16.6)§
Endometrial thickness — mm	9.4±5.7	10.7±5.9	5.1±3.5	4.3 (2.7 to 6.0)§ 5.6 (4.0 to 7.3)§
				3.3 (2.6 to 4.2)§¶ 2.9 (2.3 to 3.7)§¶

* Plus–minus values are means ±SD. In the per-protocol population, all confidence intervals in analyses of efficacy are for noninferiority. In the safety population, all confidence intervals and P values are for superiority and have been adjusted for multiple comparisons (Bonferroni correction). IQR denotes interquartile range.
† One patient had a missing score on the pictorial blood-loss assessment chart.
‡ A lower limit of the confidence interval of more than −20% (the prespecified noninferiority margin) indicates noninferiority. A lower limit of the confidence interval of more than zero indicates superiority.
§ P<0.001.
¶ The value is the ratio of the geometric mean for ulipristal acetate to the geometric mean for leuprolide acetate.

We conducted efficacy analyses in both the modified intention-to-treat and per-protocol populations. The modified intention-to-treat analyses did not include five patients: two patients (one in each ulipristal-acetate group) who never received the study drug and were not followed and three patients (one who was assigned to receive 10 mg of ulipristal acetate and two in the leuprolide-acetate group) with missing efficacy data after baseline. The per-protocol population (which consisted of the modified intention-to-treat population with the exclusion of patients with major protocol deviations and a compliance rate of <80%) was of primary interest, since a noninferiority analysis that is based on the modified intention-to-treat population is deemed to be not conservative. Analyses were based on the lower limit of two-sided 95% confidence intervals. We conducted safety analyses for superiority in the safety population (treated patients); all safety analyses were two-sided, and a P value of less than 0.05 was considered to indicate statistical significance. Since planned analyses involved comparisons of two doses of ulipristal acetate versus leuprolide acetate, a Bonferroni correction was used and all P values were doubled and confidence intervals were similarly adjusted. No further multiplicity adjustments were made. Data from one site (for four patients) were excluded from all analyses because of major protocol violations.

We used the uncorrected Newcombe–Wilson method to compare the primary efficacy end point (PBAC score, <75), with the null-hypothesis difference in percentages (ulipristal acetate minus leuprolide acetate) that were less than or equal to the noninferiority margin of –20%, as contrasted with the alternative-hypothesis difference in percentages of more than –20%. Missing data for week 13 were imputed with the use of data for the last available 28 days during treatment. A sensitivity analysis in the modified intention-to-treat population (including three patients without any on-treatment efficacy data) was performed with the use of baseline data carried forward. For coprimary safety end points, the serum estradiol level was tested through a repeated-measures analysis of covariance after log transformation of the data, and the proportion of patients reporting moderate-to-severe hot flashes was tested with the use of a Cochran–Mantel–Haenszel test. Secondary end points were analyzed with the use of the Newcombe–Wilson method for binary end points,

analysis of variance methods for the parametric analyses, and the Hodges–Lehmann estimator with corresponding Moses confidence intervals for nonparametric analyses.

RESULTS

PATIENTS

Demographic and baseline characteristics were balanced among the three study groups (Table 1, and Table 2 in the Supplementary Appendix).

EFFICACY

Primary End Point

In the per-protocol population, the proportions of patients with controlled bleeding at week 13 (PBAC score, <75 for the preceding 4 weeks) were 90% in the group receiving 5 mg of ulipristal acetate, 98% in the group receiving 10 mg of ulipristal acetate, and 89% in the group receiving leuprolide acetate (Table 2, and Table 3 in the Supplementary Appendix). The differences between ulipristal acetate and leuprolide acetate were 1.2 percentage points (95% confidence interval [CI], –9.3 to 11.8) for the 5-mg group and 8.8 percentage points (95% CI, 0.4 to 18.3) for the 10-mg group, indicating noninferiority for both doses of ulipristal acetate in controlling bleeding, since the lower limit of the confidence interval for each comparison was more than the prespecified noninferiority margin of –20%. These results were similar to those in the modified intention-to-treat analysis (Table 4 in the Supplementary Appendix). A subsequent superiority analysis comparing each ulipristal group with the leuprolide group showed that the 10-mg dose of ulipristal was superior to leuprolide acetate for this end point (P=0.03).

Secondary End Points

All treatments reduced the volume of the three largest fibroids, with median reductions at week 13 of 36% in the group receiving 5 mg of ulipristal acetate, 42% in the group receiving 10 mg of ulipristal acetate, and 53% in the group receiving leuprolide acetate (Table 2). Leuprolide acetate was associated with a significantly greater reduction in uterine volume (47%) than was either ulipristal group (20 to 22%).

Median PBAC scores at week 13 were 0 for all treatment groups. Excessive bleeding was controlled significantly more rapidly in patients receiving either 5 mg or 10 mg of ulipristal acetate than in those receiving leuprolide acetate (P<0.001 for both comparisons). In addition, amenorrhea was induced more rapidly in patients receiving 10 mg of ulipristal acetate than in those receiving leuprolide acetate (P<0.001) (Fig. 2). All study groups showed similar improvements in pain, quality of life, and hemoglobin levels (Table 2).

After the end of treatment, approximately half the patients had surgery (Fig. 1). Similar proportions of patients who did not undergo surgery in each group maintained improvements in bleeding, pain, and quality of life during follow-up without treatment (Table 5 in the Supplementary Appendix). For patients who did not undergo hysterectomy or myomectomy, ulipristal acetate showed a more sustained effect on the reduction of myoma volume during the following 6 months without treatment than did leuprolide acetate (Fig. 2 in the Supplementary Appendix). Menstruation returned on average 31 to 34 days after the end of treatment in the ulipristal groups and after 43 days in the leuprolide group.

SAFETY AND ADVERSE EVENTS

Primary End Points

At week 13, median estradiol values were 64.0 pg per milliliter (234 pmol per liter) in the group receiving 5 mg of ulipristal acetate and 60.5 pg per milliliter (222 pmol per liter) in the group receiving 10 mg of ulipristal acetate but had decreased to postmenopausal levels in the leuprolide group (25.0 pg per milliliter [92 pmol per liter]) (P<0.001 for each ulipristal group vs. leuprolide acetate) (Table 2). The proportions of patients reporting moderate-to-severe hot flashes were 11% in the group receiving 5 mg of ulipristal acetate, 10% in the group receiving 10 mg of ulipristal acetate, and 40% in the group receiving leuprolide acetate (P<0.001 for both comparisons) (Fig. 3 in the Supplementary Appendix).

Secondary End Points

There were no significant differences between the ulipristal groups and the leuprolide group in the proportion of patients reporting other adverse events or discontinuing treatment because of adverse events (Table 3, and Table 6 in the Supplementary Appendix).

The median level of type 1 CTX (but not of the other bone-resorption markers P1NP, BSAP, or DPD) was significantly greater for the leuprolide group than for either ulipristal group at week

13 (P<0.001 for both comparisons) (Table 7 in the Supplementary Appendix).

At week 13, there were no clinically relevant differences among groups in corticotropin, thyrotropin, prolactin, or aminotransferase levels. There were transient increases in mean levels of total cholesterol (greater in the leuprolide group than in the ulipristal groups) during treatment. There were no significant between-group differences in blood pressure and heart rate at week 13 (Table 7 in the Supplementary Appendix).

At week 13, mean endometrial thicknesses were 9.4 mm in the group receiving 5 mg of ulipristal acetate, 10.7 mm in the group receiving 10 mg of ulipristal acetate, and 5.1 mm in the group receiving leuprolide acetate (P<0.001 for both comparisons) (Table 2). (Additional data are provided in Table 7 in the Supplementary Appendix.)

Endometrial-biopsy examinations showed no findings of clinical concern. At week 13, all histologic specimens showed benign endometrium except for one patient in the group receiving 5 mg of ulipristal acetate, whose specimen showed simple hyperplasia. There were no findings of adenocarcinoma or premalignant lesions. Nonphysiologic endometrial changes were observed in 58% of patients receiving 5 mg of ulipristal acetate, 59% of those receiving 10 mg of ulipristal acetate, and 12% of those receiving leuprolide acetate. At week 38, after 6 months of treatment-free follow-up among women who did not undergo hysterectomy or endometrial ablation, the frequency of nonphysiologic endometrial changes was low and similar in the three study groups (6 to 7%); all histologic specimens showed benign endometrium, except for one patient (in the leuprolide group) with simple hyperplasia.

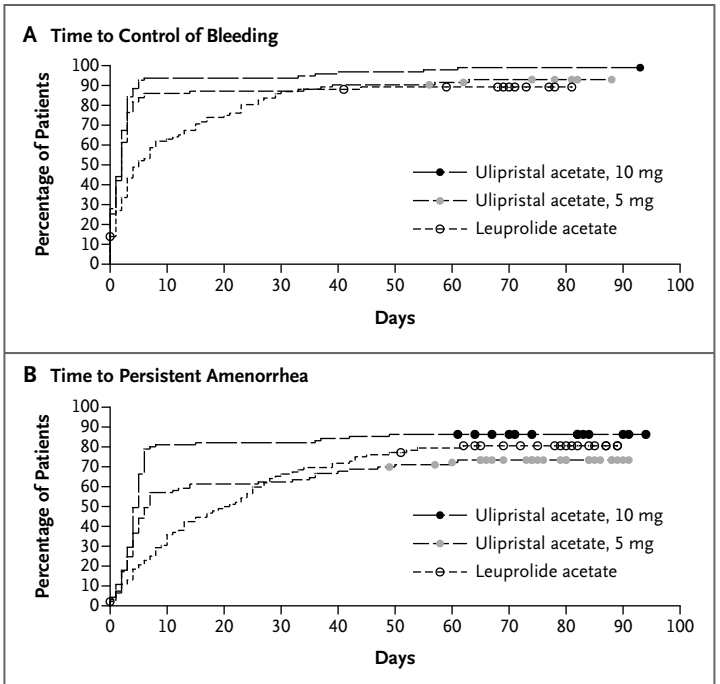

Figure 2. Kaplan–Meier Estimates of Times to the Control of Bleeding and Persistent Amenorrhea.

Panel A shows the time to the control of bleeding, which was defined as a score of less than 75 on the pictorial blood-loss assessment chart (PBAC), the primary efficacy end point. The time to the control of bleeding was defined by the first day for which the total PBAC score for the following 28 days and for all subsequent 28-day periods (recalculated day by day) up to the end of treatment was less than 75. Panel B shows the time to persistent amenorrhea (PBAC score, ≤2), a secondary efficacy end point. The time to amenorrhea was defined by the first day for which the total PBAC score for the following 28 days and for all subsequent 28-day periods (recalculated day by day) up to the end of treatment was 2 or less. Circles denote censored observations (i.e., a patient had fewer than 28 days at the end of treatment for which the total PBAC score met the criterion). Data are shown for the per-protocol population.

DISCUSSION

In our study, we showed that the use of daily oral ulipristal acetate at doses of both 5 mg and 10 mg was noninferior to once-monthly injections of leuprolide acetate in reducing bleeding associated with fibroids in patients planning surgery. All three study groups had a good response to treatment, with PBAC scores of less than 75 (the primary efficacy end point) at week 13 in 90% of patients receiving 5 mg of ulipristal acetate, 98% of those receiving 10 mg of ulipristal acetate, and 89% of those receiving leuprolide acetate.

All three treatments reduced uterine volume, although this decrease was significantly greater in the leuprolide group than in the ulipristal groups. In all three groups, there was a reduction in the total volume of the three largest fibroids, with no significant between-group differences. In exploratory analyses in the subpopulation of patients who did not undergo surgery, fibroids began to enlarge approximately 1 month after the last dose of leuprolide acetate. However, fibroid volume reduction in patients receiving ulipristal acetate appeared to be maintained in the majority of patients for 6 months after the end of treatment. We speculate that this finding may relate to apoptosis of leiomyoma cells.[26-33]

Table 3. Adverse Events (Safety Population).*

Adverse Event	Ulipristal Acetate		Leuprolide Acetate (N=101)
	5-mg Dose (N=97)	10-mg Dose (N=103)	
	number of patients (percent)		
Serious adverse events			
At least one event	8 (8)	5 (5)	6 (6)
Any event during treatment	2 (2)	1 (1)	2 (2)
Headache	1 (1)	0	0
Fibroid protruding through cervix	0	1 (1)	0
Lung infection	0	0	1 (1)
Thyroid cancer	1 (1)	0	0
Uterine hemorrhage	0	0	1 (1)
Within 4 wk after treatment†	3 (3)	3 (3)	2 (2)
From wk 17 to 38‡	3 (3)	1 (1)	2 (2)
Adverse events			
Leading to study-drug discontinuation§	1 (1)	2 (2)	6 (6)
At least one event¶	75 (77)	79 (77)	85 (84)
Hot flash	25 (26)	25 (24)	66 (65)
Headache	25 (26)	19 (18)	29 (29)
Procedural pain	9 (9)	15 (15)	9 (9)
Abdominal pain	6 (6)	11 (11)	14 (14)
Nausea	6 (6)	7 (7)	6 (6)
Fatigue	4 (4)	7 (7)	3 (3)
Anemia	5 (5)	3 (3)	5 (5)
Nasopharyngitis	6 (6)	4 (4)	2 (2)
Acne	0	5 (5)	5 (5)
Breast pain or tenderness	5 (5)	3 (3)	2 (2)
Influenza	2 (2)	2 (2)	5 (5)
Insomnia	2 (2)	2 (2)	5 (5)
Pharyngitis	5 (5)	0	2 (2)

* Listed are all serious adverse events and adverse events that occurred in at least 5% of patients in each study group, including events that were considered to be unrelated to the study drug. There were no significant between-group differences for any adverse event except hot flashes ($P<0.001$ for both doses of ulipristal acetate vs. leuprolide acetate). No adjustment for multiplicity was performed.

† These serious adverse events were operative complications in two patients and sarcoma in one patient (retrospectively diagnosed after further review after premature discontinuation of the study drug) in the group receiving 5 mg of ulipristal acetate; endometrial polyp, hemangioma, and uterine hemorrhage in one patient each in the group receiving 10 mg of ulipristal acetate; and operative complications and lymphocytic choriomeningitis in one patient each in the group receiving leuprolide acetate.

‡ These serious adverse events were spontaneous abortion, surgery for suspected ovarian tumor but intraoperative diagnosis corrected to new uterine myoma, and vaginal hemorrhage in one patient each receiving 5 mg of ulipristal acetate; ovarian cyst in one patient receiving 10 mg of ulipristal acetate; and uterine hemorrhage in two patients receiving leuprolide acetate.

§ Adverse events leading to the discontinuation of a study drug are listed in the Supplementary Appendix.

¶ These adverse events occurred between the first dose of a study drug and week 17 (i.e., 4 weeks after the end of treatment).

The reduction in bleeding associated with fibroids was accompanied by improvements in hemoglobin and hematocrit in all three study groups. These data are consistent with previous reports of leuprolide therapy, in which improvement in anemia was associated with decreases in fibroid and uterine volume.[34-38] Ulipristal acetate attenuated bleeding more rapidly than leuprolide acetate,

with median times to amenorrhea of 7 days in patients receiving 5 mg of ulipristal acetate, 5 days in those receiving 10 mg of ulipristal acetate, and 21 days in those receiving leuprolide acetate. Ulipristal acetate has an antiproliferative effect, but the mechanisms underlying its rapid effect on bleeding remain uncertain and may be related to direct effects on the endometrium.[12,17,19]

As with other SPRMs, ulipristal acetate induced benign endometrial changes. These findings had reversed when reassessed after 6 months without treatment, and there was no dysplasia or neoplasia identified among patients receiving ulipristal acetate. The treatments were similarly effective at reducing pain associated with fibroids and normalizing quality of life.

In both ulipristal groups, plasma estradiol levels were maintained in the midfollicular range, whereas patients in the leuprolide group had on average a significant reduction to postmenopausal levels. Consistent with these findings, moderate-to-severe hot flashes were significantly less common with ulipristal acetate than with leuprolide acetate.

We found no clinically relevant effects of ulipristal acetate and leuprolide acetate on corticotropin, thyrotropin, prolactin, or glucose levels. Four markers of bone turnover were evaluated; median levels of one (CTX) were significantly lower at the end of treatment in both ulipristal groups than in the leuprolide group ($P<0.001$ for both comparisons). This finding may indicate a higher rate of bone resorption in patients receiving leuprolide acetate than in those receiving ulipristal acetate, although we did not adjust for multiple testing.

Our study has several limitations. It was not specifically designed to assess surgical outcomes, but rates and types of surgery were similar in the three study groups (Fig. 1). As per clinical practice, uterine and fibroid volumes were not confirmed by central reading. In addition, the duration of treatment was restricted to 13 weeks. Hence, more data are needed regarding benefits and risks of long-term treatment with ulipristal acetate.

In summary, in this randomized, controlled study, we found that oral ulipristal acetate at doses of either 5 or 10 mg was noninferior to monthly injections of leuprolide acetate in controlling uterine bleeding in women with symptomatic fibroids before planned surgery and had a better side-effect profile.

Supported by PregLem.

Dr. Donnez reports receiving payment for serving on a scientific advisory board from PregLem, payment from stocks sold in October 2010 from the company's full acquisition by Gedeon Richter Group, and lecture fees from Serono, Merck, Organon, and Ferring; Dr. Bouchard, receiving payment for serving on a scientific advisory board from PregLem, payment from stocks sold in October 2010 from the company's full acquisition by Gedeon Richter Group, and lecture fees from HRA Pharma, Theramex, Pierre Fabre, and PregLem; Dr. Bestel, being an employee of PregLem and receiving payment from stocks sold in October 2010 from the company's full acquisition by Gedeon Richter Group; Dr. Terrill, being an employee of MDSL International and receiving payment to his institution for consultancy and contracted data-management and statistical support; Dr. Osterloh, receiving payment to his institution for consultancy from OsterMed; and Dr. Loumaye, being an employee of PregLem and receiving payment from stocks sold in October 2010 from the company's full acquisition by Gedeon Richter Group. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank Venkat Ramanan of PregLem for assistance with the preparation of the manuscript with the support of Tove Anderson and Nigel Eastmond of Darwin Healthcare Communications.

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