ORIGINAL ARTICLE

Ulipristal Acetate versus Placebo for Fibroid Treatment before Surgery

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ABSTRACT

BACKGROUND

The efficacy and safety of oral ulipristal acetate for the treatment of symptomatic uterine fibroids before surgery are uncertain.

METHODS

We randomly assigned women with symptomatic fibroids, excessive uterine bleeding (a score of >100 on the pictorial blood-loss assessment chart [PBAC, an objective assessment of blood loss, in which monthly scores range from 0 to >500, with higher numbers indicating more bleeding]) and anemia (hemoglobin level of ≤10.2 g per deciliter) to receive treatment for up to 13 weeks with oral ulipristal acetate at a dose of 5 mg per day (96 women) or 10 mg per day (98 women) or to receive placebo (48 women). All patients received iron supplementation. The coprimary efficacy end points were control of uterine bleeding (PBAC score of <75) and reduction of fibroid volume at week 13, after which patients could undergo surgery.

RESULTS

At 13 weeks, uterine bleeding was controlled in 91% of the women receiving 5 mg of ulipristal acetate, 92% of those receiving 10 mg of ulipristal acetate, and 19% of those receiving placebo ($P<0.001$ for the comparison of each dose of ulipristal acetate with placebo). The rates of amenorrhea were 73%, 82%, and 6%, respectively, with amenorrhea occurring within 10 days in the majority of patients receiving ulipristal acetate. The median changes in total fibroid volume were –21%, –12%, and +3% ($P=0.002$ for the comparison of 5 mg of ulipristal acetate with placebo, and $P=0.006$ for the comparison of 10 mg of ulipristal acetate with placebo). Ulipristal acetate induced benign histologic endometrial changes that had resolved by 6 months after the end of therapy. Serious adverse events occurred in one patient during treatment with 10 mg of ulipristal acetate (uterine hemorrhage) and in one patient during receipt of placebo (fibroid protruding through the cervix). Headache and breast tenderness were the most common adverse events associated with ulipristal acetate but did not occur significantly more frequently than with placebo.

CONCLUSIONS

Treatment with ulipristal acetate for 13 weeks effectively controlled excessive bleeding due to uterine fibroids and reduced the size of the fibroids. (Funded by PregLem; ClinicalTrials.gov number, NCT00755755.)

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Uterine leiomyomas, or fibroids, are benign, hormone-sensitive, smooth-muscle tumors that occur in 20 to 40% of women of reproductive age.[1,2] The most common symptoms are menorrhagia and iron-deficiency anemia, which may lead to chronic fatigue[3] that may not be adequately controlled with iron supplementation alone.[4-6] Other symptoms include pelvic pain, dysmenorrhea, and pressure effects, which may adversely affect quality of life and fertility.[7-10]

Many patients require intervention, and the choice of treatment is guided by the patient's age and desire to preserve fertility and avoid hysterectomy.[10] Fibroids are the most common indication for hysterectomy.[1] Other treatments include myomectomy, hysteroscopic removal, uterine-artery embolization, and various other interventions performed under radiologic guidance.[10,11]

Medical therapies are also available, but these therapies have limitations. Gonadotropin-releasing hormone (GnRH) agonists can be used as bridging or presurgical treatments and create an artificial menopausal state, resulting in reversible reduction of uterine and fibroid volume and aiding in the correction of anemia[12-16]; however, GnRH agonists frequently cause hot flashes, and the use of these drugs is approved only for short-term therapy because of safety concerns (loss of bone mineral density). Progestins are often associated with breakthrough bleeding that limit their use,[17] and they may promote proliferation of fibroids.[18-21] The levonorgestrel-releasing intrauterine system can be used in patients who do not have large uteri distorted by fibroids, but irregular bleeding is frequent, expulsion of the intrauterine device is more common than in women without fibroids, and the effect on fibroid volume is controversial.[22]

The role of progesterone in promoting the growth of fibroids has stimulated interest in modulating the progesterone pathway. Results from small pilot studies and other uncontrolled trials in which selective progesterone-receptor modulators such as asoprisnil, mifepristone, telapristone, and ulipristal acetate were used have suggested the potential benefit of these agents in patients with fibroids.[23-26]

Ulipristal acetate is a selective progesterone-receptor modulator that acts on progesterone receptors in myometrial and endometrial tissue and inhibits ovulation without causing large effects on estradiol levels or antiglucocorticoid activity.[27,28] In two small, phase 2 studies (one involving 18 patients and one involving 38 patients), a 3-month course of ulipristal acetate at a dose of 10 mg per day or 20 mg per day reduced abnormal bleeding and significantly decreased fibroid volume; there was no advantage of the 20-mg dose over the 10-mg dose. We conducted the PGL4001 (Ulipristal Acetate) Efficacy Assessment in Reduction of Symptoms Due to Uterine Leiomyomata (PEARL I) trial to determine the effects of 5 mg of ulipristal acetate per day and 10 mg of ulipristal acetate per day on uterine bleeding and fibroid volume in women with symptomatic fibroids who were planning to undergo surgery.

METHODS

STUDY DESIGN AND OVERSIGHT

We conducted this randomized, parallel-group, double-blind, placebo-controlled, phase 3 trial from October 2008 through August 2010 at 38 academic research centers in six countries. The study was approved by the independent ethics committee at each participating site and was conducted in accordance with the International Conference on Harmonization Good Clinical Practice guidelines. The original protocol, amendments, and statistical analysis plan are available with the full text of this article at NEJM.org. The study was designed by the sponsor (PregLem) with involvement of the academic investigators and trial statistician. The data were collected by an independent contract research organization (ICON Clinical Research) and were handled 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 support that was funded by the sponsor, and all the authors made the decision to submit the manuscript for publication. The first author vouches for the accuracy of the data and the analyses and for the fidelity of the study to the protocol.

STUDY POPULATION

Women 18 to 50 years of age were eligible if they met the following criteria: a score on the pictorial blood-loss assessment chart (PBAC, in which monthly scores range from 0 to >500, with higher numbers indicating more bleeding) higher than 100 during days 1 to 8 of menstruation; fibroid-related anemia, defined as a hemoglobin level of

10.2 g per deciliter or lower without macrocytosis; a myomatous uterus with a size equivalent to that of a uterus at 16 weeks or less of gestation; at least one fibroid that was 3 cm or more in diameter, but with no fibroid measuring more than 10 cm in diameter, as measured by ultrasonography; and a body-mass index (the weight in kilograms divided by the square of the height in meters) of 18 to 40. All patients were eligible to undergo fibroid surgery after the end of the treatment period. Written informed consent was obtained from all patients. The main exclusion criteria are listed in Table 1 in the Supplementary Appendix, available at NEJM.org.

RANDOMIZATION AND INTERVENTION

Patients were randomly assigned, in a 2:2:1 ratio, to receive 5 mg of ulipristal acetate per day, 10 mg of ulipristal acetate per day, or placebo (one pill per day, provided by PregLem). Randomization was stratified according to the hematocrit level at screening (≤28% or >28%) and race (black or other). The investigator assigned patients to a study group with the use of a Web-integrated interactive voice-response system. Study materials and medication packaging were identical for all three groups.

Treatment was initiated during the first 4 days of menstruation. All patients received 80 mg of iron supplementation (256.3 mg of ferrous sulfate [Tardyferon, Pierre Fabre Pharma]) once daily during the active-treatment phase. In addition, iron could be prescribed during the screening and follow-up periods at the discretion of the investigator.

After week 13, patients could undergo surgery according to the clinical judgment of the investigator, but no further pharmacologic treatment of fibroids was administered. Follow-up visits were conducted at weeks 17, 26, and 38.

ASSESSMENT OF UTERINE BLEEDING

Menstrual bleeding was assessed with the use of the PBAC,[29] a validated method used to objectively estimate blood loss. Monthly scores range from 0 (amenorrhea) to more than 500, with higher numbers indicating more bleeding. Patients were provided with standardized sanitary materials and recorded the numbers of tampons or pads they used and the extent of soiling with blood (see the Supplementary Appendix for a sample PBAC and an example of the calculation of the score). Menorrhagia was defined as a PBAC score of more than 100 during one menstrual period, which corresponds to a blood loss of more than 80 ml. A PBAC score of 400 corresponds to a blood loss of approximately 300 ml or the use of approximately 80 tampons or pads.[29]

At screening, patients were taught to use the PBAC and were asked to complete it daily throughout the treatment period up to week 13 and for 28 days preceding the post-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.

END POINTS

The coprimary efficacy end points were the percentage of patients with a reduction in uterine bleeding at week 13, defined as a PBAC score (summed over the preceding 28-day period) of less than 75, and the change in total fibroid volume from screening to week 13, as assessed by magnetic resonance imaging (MRI) and read centrally by a radiologist who was unaware of the study-group assignments. The total fibroid volume was the sum of the individual fibroid volumes.

Secondary end points included the bleeding pattern (consecutive 28-day PBAC scores); amenorrhea (PBAC 28-day score of ≤2 at weeks 9 and 13); reduction in uterine and fibroid volume (i.e., the percentages of women with at least a 25% reduction); changes in hemoglobin, hematocrit, and ferritin levels; pain, as measured with the use of the Short-Form McGill Pain Questionnaire[30] (which includes a questionnaire on which scores range from 0 to 45, with higher scores indicating more severe pain, as well as a visual-analogue scale ranging from 0 to 100, with higher scores indicating more severe pain); and quality of life (as measured by a questionnaire assessing discomfort associated with uterine fibroids (in which scores range from 0 to 28, with higher scores indicating more discomfort; see the Supplementary Appendix). The efficacy analyses were based on the 13-week measurements; results from additional time points are reported in the Supplementary Appendix.

ASSESSMENT OF ADVERSE EVENTS

The frequency and severity of adverse events (spontaneously reported or elicited by the investigators with the use of nonleading questions) were record-

Table 1. Baseline Characteristics of the Modified Intention-to-Treat Population.*

Characteristic	Placebo (N=48)	Ulipristal Acetate, 5 mg (N=95)	Ulipristal Acetate, 10 mg (N=94)
Age — yr	41.6±5.6	41.2±5.9	42.0±5.6
Race — no. (%)†			
White	41 (85)	84 (88)	85 (90)
Asian	7 (15)	11 (12)	9 (10)
Weight — kg	64.7±12.5	70.1±13.6	67.2±10.3
Body-mass index‡	24.6±4.4	25.9±4.6	25.0±4.0
PBAC score§			
Median	376	386	330
Interquartile range	241–608	235–627	235–537
Total fibroid volume at screening — cm^3			
Median	61.9	100.7	96.7
Interquartile range	24.8–158.9	40.0–205.3	31.7–181.3
Fibroid type — no./total no. (%)¶			
Submucosal	25/45 (56)	50/89 (56)	41/82 (50)
Intramural	36/45 (80)	58/89 (65)	59/82 (72)
Subserosal	9/45 (20)	25/89 (28)	33/82 (40)
Subserosal only	1/45 (2)	4/89 (4)	5/82 (6)
Uterine volume at screening — cm^3			
Median	318.8	337.6	325.6
Interquartile range	216.0–496.3	236.1–502.8	212.6–453.3
Uterine cavity deformation — no./total no. (%)	41/47 (87)	75/92 (82)	65/88 (74)
Hemoglobin — g/dl	9.55±1.18	9.32±1.50	9.46±1.57
Assessment of pain			
Short-Form McGill Pain Questionnaire‖			
Median	8.5	6.5	8.0
Interquartile range	3.0–18.0	3.0–15.0	4.0–16.0
Visual-analogue scale**			
Median	49.5	39.0	39.0
Interquartile range	16.5–74.0	15.0–64.0	19.0–60.0
Measurement of discomfort questionnaire††			
Median	16.0	14.0	14.5
Interquartile range	13.5–18.0	10.0–19.0	11.0–18.0

* Plus–minus values are means ±SD. There were no significant differences in baseline characteristics between either ulipristal group and the placebo group.
† Race was determined by the site investigator.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.
§ The pictorial blood-loss assessment chart (PBAC) is a validated method used to objectively estimate blood loss. Monthly scores range from 0 (amenorrhea) to more than 500, with higher numbers indicating more bleeding.
¶ Patients could have more than one type of fibroid.
‖ Scores on the Short-Form McGill Pain Questionnaire range from 0 to 45, with higher scores indicating more severe pain.
** Scores on the visual-analogue scale range from 0 to 100, with higher scores indicating more severe pain.
†† Scores on the measurement of discomfort questionnaire range from 0 to 28, with higher scores indicating greater discomfort.

ed on standard forms at every visit up to the visit at week 17. Serious adverse events were recorded up to week 38. In addition, adverse events occurring more than 4 weeks after the end of the treatment period were recorded if they were considered to be related to the protocol or study drug or involved uterine hemorrhage. Endometrial thickness was measured by MRI at screening, at week 13, and (if

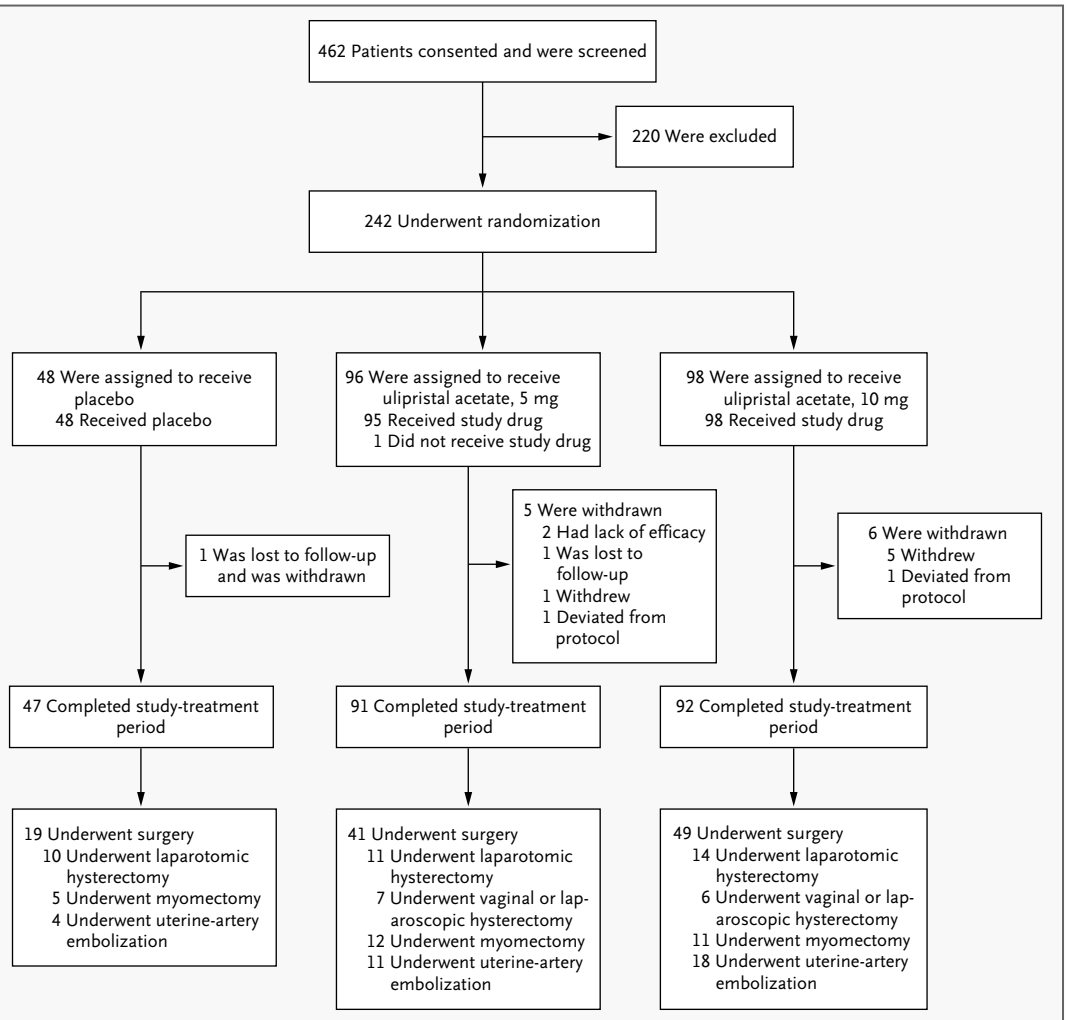

Figure 1. Screening, Randomization, and Follow-up.

One patient in the 5-mg ulipristal acetate group (who did not receive any dose of study drug) and four patients in the 10-mg ulipristal acetate group were excluded from the primary analysis because they did not have any efficacy data.

no hysterectomy or endometrial ablation was performed) at weeks 26 and 38.

OTHER ASSESSMENTS

Endometrial biopsy samples were obtained at screening, at week 13, and at week 38 if no hysterectomy or endometrial ablation was performed. All biopsy samples were processed at a central location and were assessed by three independent pathologists who were unaware of the study-group assignments, the visit sequence, and one another's assessment. Assessments were made according to standard diagnostic criteria[31] and terminology for nonphysiological endometrial changes (progesterone-receptor modulator–associated endometrial changes), as described previously by Mutter and colleagues.[32]

Serum estradiol, progesterone, corticotropin, thyrotropin, and prolactin levels were measured at baseline and at weeks 5, 9, 13, and 17; hematologic, coagulation, and biochemical variables and lipid and glucose levels were measured at all visits. The follicle-stimulating hormone level was measured at baseline and at week 13.

STATISTICAL ANALYSIS

Efficacy analyses were performed according to the intention-to-treat principle. We excluded one patient in the 5-mg ulipristal acetate group who was withdrawn before she received any study drug. All

Table 2. Key Efficacy End Points in the Modified Intention-to-Treat Population.*

End Point	Placebo (N=48)	Ulipristal Acetate, 5 mg (N=95)	Difference, 5 mg Ulipristal Acetate–Placebo (95% CI)†	P Value	Ulipristal Acetate 10 mg (N=94)	Difference, 10 mg Ulipristal Acetate–Placebo (95% CI)†	P Value
Primary end points at wk 13							
PBAC <75 — no./total no. (%)	9/48 (19)	86/94 (91)	73 (55 to 83)	<0.001	86/93 (92)	74 (56 to 84)	<0.001
% Change from screening in total fibroid volume‡				0.002			0.006
Median	3.0	−21.2	−22.6 (−36.1 to −8.2)		−12.3	−18.2 (−33.0 to −5.2)	
Interquartile range	−19.7 to 23.0	−41.2 to −1.1			−39.1 to 4.3		
Secondary end points							
Baseline PBAC							
Median	376	386			330		
Interquartile range	241 to 608	235 to 627			235 to 537		
Wk 9–12 PBAC							
Median	336	0			0		
Interquartile range	115 to 543	0 to 5			0 to 0		
Change from baseline to wk 9–12 in PBAC							
Median	−59	−329	−291 (−399 to −194)	<0.001	−326	−287 (−371 to −198)	<0.001
Interquartile range	−216 to 58	−571 to −205			−527 to −226		
Amenorrhea, PBAC ≤2, at wk 9–12 — no./total no. (%)	3/48 (6)	69/94 (73)	67 (50 to 77)	<0.001	76/93 (82)	76 (59 to 84)	<0.001
Total reduction ≥25% in fibroid volume at wk 13 — no./total no. (%)	8/45 (18)	35/85 (41)	23 (4 to 39)	0.01	33/80 (41)	24 (4 to 39)	0.01
% Change from screening in uterine volume at wk 13				0.001§			0.003§
Median	5.9	−12.1			−12.0		
Interquartile range	−3.8 to 18.4	−28.3 to 2.9			−27.7 to 6.1		
Reduction in uterine volume ≥25% at wk 13 — no./total no. (%)	3/47 (6)	30/88 (34)	28 (11 to 40)	<0.001	24/85 (28)	22 (6 to 35)	0.006

Hemoglobin — g/dl							
Baseline	9.55±1.18	9.32±1.50			9.46±1.57		
Wk 13	12.61±1.30	13.50±1.32			13.60±1.18		
Change from baseline to wk 13	3.10±1.68	4.25±1.90	0.92 (0.39 to 1.44)	<0.001	4.20±1.83	1.00 (0.48 to 1.52)	<0.001
Pain assessment with Short-Form McGill Pain Questionnaire							
Baseline							
Median	8.5	6.5			8.0		
Interquartile range	3.0 to 18.0	3.0 to 15.0			4.0 to 16.0		
Wk 13							
Median	4.2	1.0			1.0		
Interquartile range	1.0 to 10.0	0.0 to 4.0			0.0 to 4.0		
Change from baseline to wk 13							
Median	−2.5	−5.0	−2.0 (−4.0 to 0.0)	0.10	−5.6	−3.0 (−5.0 to 0.0)	0.04
Interquartile range	−6.3 to 1.0	−8.0 to −2.0			−11.0 to −2.0		
Measurement of discomfort questionnaire							
Baseline							
Median	16.0	14.0			14.5		
Interquartile range	13.5 to 18.0	10.0 to 19.0			11 to 18		
Wk 13							
Median	11.0	3.0			4.0		
Interquartile range	4.0 to 15.0	1.0 to 7.0			2.0 to 7.0		
Change from baseline to wk 13							
Median	−6.0	−9.0	−4.0 (−6.0 to −1.0)	0.001	−11.0	−4.0 (−7.0 to −2.0)	<0.001
Interquartile range	−9.0 to −2.0	−13.0 to −6.0			−14.0 to −5.0		

* All confidence intervals and P values have been adjusted for multiplicity (Bonferroni correction) because two doses of ulipristal acetate were compared with placebo (i.e., P values were multiplied by 2). PBAC denotes pictorial blood-loss assessment chart.
† The differences in categories with numbers and percents are percentage-point differences. The differences in categories with medians and interquartile ranges are differences in medians, as calculated with the use of the Hodges–Lehmann estimator.
‡ The percent change from screening in total fibroid volume was assessed in 45 patients in the placebo group, 85 patients in the 5-mg ulipristal acetate group, and 80 patients in the 10-mg ulipristal acetate group.
§ The statistical testing was performed on log-transformed data.

the statistical tests were two-sided, with a 5% level of significance. Since the planned analyses involved comparisons of two doses of ulipristal acetate with placebo, a Bonferroni correction was used (all P values were doubled). No further adjustments for multiplicity have been made, since the efficacy outcome for each dose group was considered to be successful only if there were significant improvements over placebo in both coprimary efficacy end points. In general, missing values were imputed for the statistical analyses with the use of the last available post-baseline value up to the time point of interest. We performed a sensitivity analysis that included four patients, all in the 10-mg ulipristal acetate group, who did not have any efficacy data while receiving treatment, using baseline data carried forward.

The percentages of patients with a PBAC of less than 75 at week 13 were compared with the use of a Cochran–Mantel–Haenszel test (with adjustment for randomization strata), with confidence intervals calculated with the use of the Newcombe–Wilson score method (uncorrected).[33] Additional binary end points were analyzed in a similar way. For the coprimary end point of the change in total fibroid volume, the data did not meet the assumptions of parametric tests and were analyzed with the use of the van Elteren extension to the Wilcoxon rank-sum test with adjustment for randomization strata, with the Hodges–Lehmann estimator (and corresponding Moses confidence interval) used for the differences in medians.[34] The changes from baseline in PBAC scores and in pain assessments were analyzed in a similar way. Data on uterine volume were log-transformed and were evaluated with the use of an analysis of covariance; hemoglobin and hematocrit values were analyzed with the use of a repeated-measures analysis of covariance, with adjustment for the value at screening and for randomization strata in all analyses.

The estimations of the sample size were based on the end point of change in fibroid volume, since more subjects were needed to show a significant treatment-related difference between the active-treatment groups and the placebo group for this end point than for the bleeding end point. Assuming a 10% dropout rate, we estimated that 240 patients would have to undergo randomization (96 in each ulipristal acetate group and 48 in the placebo group) for the study to have 90% power to show a significant between-group difference, assuming an average difference of −0.1 (approximately 20% change from baseline) in the change in $\log_{10}$ total fibroid volume between the ulipristal acetate groups and the placebo group and a between-patient standard deviation of 0.15.

RESULTS

PATIENTS

The baseline characteristics of the modified intention-to-treat population are shown in Table 1. There were no significant differences between the ulipristal acetate groups and the placebo group. The screening, randomization, and follow-up of the patients are shown in Figure 1.

PRIMARY EFFICACY END POINTS

Menstrual bleeding was controlled in 91% of the women who received 5 mg of ulipristal acetate and in 92% of the women who received 10 mg of ulipristal acetate, as compared with only 19% of the women who received placebo (P<0.001 for the comparison of each ulipristal acetate group with the placebo group) (Table 2). There were statistically and clinically significant reductions in fibroid volumes in both ulipristal acetate groups as compared with the placebo group (Table 2). Further analyses in the modified intention-to-treat population (with baseline data carried forward) and in the per-protocol population (all patients who completed the assigned regimen without major deviations from the protocol) showed similar results (see the Supplementary Appendix).

SECONDARY END POINTS

There were large reductions in bleeding (median changes in PBAC score of >300) in the patients who received either dose of ulipristal acetate, whereas there was little change in the patients who received placebo (P<0.001 for the comparison of each ulipristal acetate group with the placebo group at weeks 5 to 8 and 9 to 12). The majority of patients in the ulipristal acetate groups, but few patients in the placebo group, had amenorrhea after 4 weeks of receipt of the study drug (P<0.001 for the comparison of each ulipristal acetate group with the placebo group). Approximately 50% of the patients in the 5-mg ulipristal acetate group and 70% of the patients in the 10-mg group became amenorrheic within the first 10 days (Fig. 2). Excessive bleeding was rapidly controlled (as defined by subsequent PBAC scores that were always <75) by day 8 in more than 75% of the patients receiving ulipristal acetate, as compared with 6% receiving placebo (Fig. 2).

The percentage of patients with a hemoglobin level higher than 12 g per deciliter and a hematocrit level higher than 36% increased over time in all groups. Hemoglobin and hematocrit levels were significantly higher in both ulipristal acetate groups than in the placebo group at all time points after the initiation of treatment (see the Supplementary Appendix).

A significantly greater percentage of patients in both ulipristal acetate groups than in the placebo group had a reduction in fibroid volume of at least 25% (P=0.01) and a reduction in uterine volume of at least 25% at week 13 (P<0.001 for the difference in volumes with 5 mg of ulipristal acetate as compared with placebo, and P=0.006 for the difference in volumes with 10 mg of ulipristal acetate as compared with placebo). As compared with placebo, both doses of ulipristal acetate led to reductions in pain (especially moderate or severe pain), as measured with the use of the Short-Form McGill Pain Questionnaire (Table 2, and the Supplementary Appendix).

EFFICACY EVALUATIONS AFTER WEEK 13

Approximately half the patients in each group underwent fibroid surgery after completing the study-treatment phase (see Fig. 1 for the numbers and types of surgeries performed). Efficacy results for patients who did not undergo surgery during the post-treatment follow-up phase are provided in the Supplementary Appendix. Menstruation occurred at a mean of 30 days after the end of treatment with ulipristal acetate.

SAFETY AND SIDE-EFFECT PROFILE

The rate of the occurrence of any adverse events did not differ significantly among the three groups. Headache and pain, discomfort, or tenderness in the breasts were the most common adverse events in the ulipristal acetate groups, but the events did not occur significantly more frequently in these groups than in the placebo group (Table 3). The rate of hot flashes was low (<3%) in all groups.

Two serious adverse events occurred during the treatment period: one event of a fibroid protruding through the cervix (in the placebo group) and one event of uterine hemorrhage (in the 10-mg ulipristal acetate group). Three serious adverse events occurred within 1 month after the beginning of the follow-up period: one diagnosis of breast cancer (in the placebo group) and one event each of ovarian hemorrhage and uterine hemorrhage (both in the 5-mg ulipristal acetate group). Two serious adverse events occurred during further follow-up to 6 months: one event of menometrorrhagia (in the placebo group) and one event of uterine hemorrhage (in the 10-mg ulipristal acetate group) (Table 3).

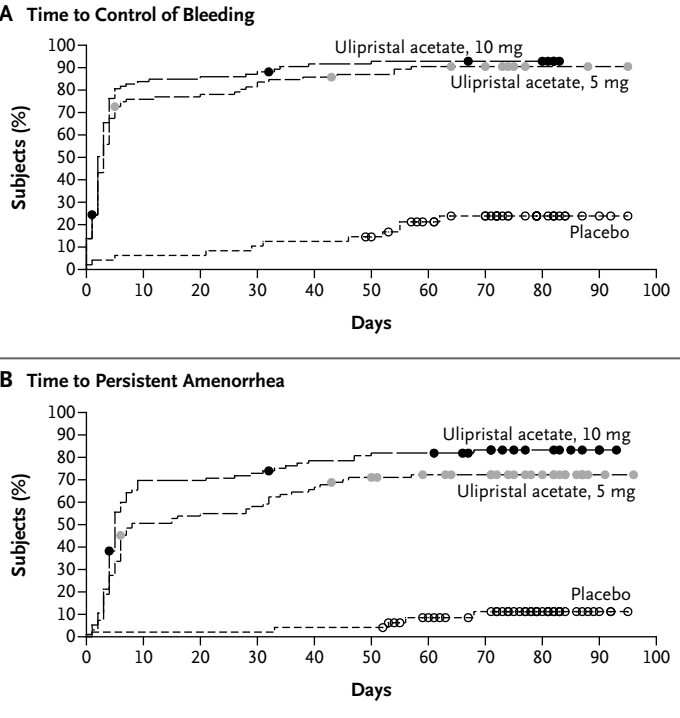

Figure 2. Time to Control of Bleeding and Persistent Amenorrhea.
Control of bleeding was defined as a score on the pictorial blood-loss assessment chart (PBAC) of less than 75; monthly PBAC scores range from 0 (amenorrhea) to more than 500, with higher numbers indicating more bleeding and with menorrhagia defined as a PBAC score of more than 100 during one menstrual period, corresponding to a blood loss of more than 80 ml. The time to control of bleeding (Panel A) was defined by the first day for which the total PBAC score for all subsequent 28-day periods up to the end of the treatment period was less than 75. Persistent amenorrhea was defined as a PBAC score of 2 or less. The time to amenorrhea (Panel B) was defined by the first day for which the total PBAC score for all subsequent 28-day periods up to the end of the treatment period was 2 or less. Day 0 represents the first day of treatment. Circles denote censored observations (i.e., a patient had fewer than 28 days at the end of the treatment period for which the total PBAC score met the criterion).

Levels of low-density and high-density lipoprotein cholesterol rose during the treatment period in all groups; the increases were slightly greater in the ulipristal acetate groups than in the placebo group, but they were modest in all groups (see the Supplementary Appendix). There were no consistent significant differences in glucose, estradiol, corticotropin, or prolactin levels between the ulipristal acetate groups and the placebo

Table 3. Adverse Events in the Safety Population.*

Event	Placebo (N=48)	Ulipristal Acetate, 5 mg (N=95)	Ulipristal Acetate, 10 mg (N=98)
		number of patients (percent)	
At least one serious adverse event	3 (6)	2 (2)	2 (2)
Serious adverse event during treatment period	1 (2)	0	1 (1)
Uterine hemorrhage	0	0	1 (1)
Fibroid protruding through cervix	1 (2)	0	0
Serious adverse event within 4 wk after treatment period	1 (2)	2 (2)	0
Uterine hemorrhage	0	1 (1)	0
Breast cancer	1 (2)	0	0
Ovarian hemorrhage	0	1 (1)	0
Serious adverse event from wk 17 to wk 38	1 (2)	0	1 (1)
Menometrorrhagia	1 (2)	0	0
Uterine hemorrhage	0	0	1 (1)
Adverse event leading to discontinuation of study drug†	1 (2)	1 (1)	1 (1)
At least one adverse event‡	22 (46)	47 (49)	52 (53)
Headache	2 (4)	4 (4)	10 (10)
Breast pain, tenderness, or discomfort	0	2 (2)	6 (6)
Abdominal pain	2 (4)	2 (2)	3 (3)
Pyrexia	2 (4)	3 (3)	2 (2)
Hypercholesterolemia	1 (2)	3 (3)	2 (2)
Hypothyroidism	0	2 (2)	4 (4)
Constipation	1 (2)	4 (4)	0
Hypertriglyceridemia	1 (2)	3 (3)	1 (1)
Influenza	1 (2)	1 (1)	3 (3)
Dizziness	0	1 (1)	3 (3)
Nasopharyngitis	0	3 (3)	0
Dysmenorrhea	2 (4)	0	0

* All serious adverse events and adverse events occurring in at least 3% of the patients in any group are included. Patients could have more than one adverse event of the same type. There were no significant differences between either ulipristal acetate group and the placebo group for any adverse event, with two-sided P values calculated with the use of Fisher's exact test and no adjustment for multiplicity.

† The adverse events leading to discontinuation of the study drug were breast cancer (one patient in the placebo group), endometrial changes (one patient in the 5-mg ulipristal acetate group, with the event initially reported by the local laboratory as hyperplasia but later diagnosed as benign endometrium by three pathologists who were unaware of the study-group assignments), and ovarian cyst (one patient in the 10-mg ulipristal acetate group).

‡ Adverse events with onset at or after the first dose of study drug and on or before the last assessment date of week 17 (4 weeks after the end of the treatment period) are included.

group. Estradiol levels after treatment with ulipristal acetate were generally consistent with midfollicular-phase levels for a premenopausal woman (60 to 150 pg per milliliter). There was no significant difference among the groups in the incidence of abnormal liver-function tests or mean endometrial thickness. A minority of patients receiving ulipristal acetate had endometrial thickness greater than 16 mm at week 13; this condition had reversed in all cases by week 26 or 38 (see the Supplementary Appendix).

At week 13, endometrial-biopsy samples that were assessed centrally revealed no malignant or premalignant lesions or hyperplasia; nonphysio-

logical endometrial changes were observed more frequently in the 5-mg and 10-mg ulipristal acetate groups than in the placebo group (62%, 57%, and 6%, respectively). At week 38 (6 months after the end of the treatment phase), these changes had disappeared; there was one case of complex atypical hyperplasia in the placebo group.

DISCUSSION

In this randomized, double-blind, placebo-controlled trial, oral ulipristal acetate at a dose of 5 mg per day or 10 mg per day was effective in controlling excessive bleeding and shrinking fibroids in patients who had severe bleeding and associated anemia at baseline. Treatment with ulipristal acetate, as compared with placebo, also resulted in clinically significant increases in hemoglobin and hematocrit levels and reductions in self-reported pain and discomfort due to fibroids.

Current medical therapies for fibroids have limitations.[4,35] Although treatment with a GnRH agonist before surgery results in a lower frequency of midline incisions, a greater likelihood of vaginal, as compared with abdominal, hysterectomy, and a reduction in intraoperative blood loss, GnRH agonists cause side effects such as hot flashes and atrophic vaginitis that may reduce adherence to therapy.[12]

Pilot and phase 2 trials have previously suggested a benefit of selective progesterone-receptor modulators for the treatment of fibroids.[23-26] This phase 3 trial involving women with fibroid-related anemia confirms and extends the findings of prior, smaller studies.[24,25]

Heavy menstrual bleeding is a major cause of doctor visits and lost work days.[6] In this study, bleeding was controlled within 8 days after the beginning of the treatment period in the majority of patients in the ulipristal acetate groups but in few patients in the placebo group. Anemia was corrected from week 5 on in significantly more patients in the ulipristal acetate groups than in the placebo group. With iron supplementation, anemia was eventually corrected in most patients in the placebo group, despite ongoing bleeding. However, iron supplements may have adverse events, and absorption is variable.[36]

Treatment with ulipristal acetate reduced fibroid volume without suppressing estradiol levels, which were in the midfollicular range in the ulipristal acetate groups. In contrast, GnRH agonists substantially reduce estrogen levels, with associated risks of bone loss[37] and hot flashes.[38] In our study, the frequency of hot flashes was similar in the ulipristal acetate and placebo groups.

Previous studies involving women treated with ulipristal acetate for up to 6 months identified cases of progesterone-receptor modulator–associated endometrial changes, including cystic glandular alterations,[24,27,32] but reversibility was not investigated. In this study, nonphysiological endometrial changes were observed more frequently in patients receiving ulipristal acetate than in patients receiving placebo, but these changes had resolved by the time of the follow-up assessment 6 months after the end of the treatment period.

A limitation of this study is that the duration of treatment was restricted to 13 weeks. More data are needed to inform the benefits and risks of long-term treatment with ulipristal acetate. Our study focused on preoperative treatment but was not designed to evaluate possible treatment-related differences in surgical outcomes.

In conclusion, treatment with ulipristal acetate (at a dose of 5 mg or 10 mg) for 13 weeks before planned surgery was effective in controlling bleeding, decreasing fibroid volume, and reducing discomfort in women with menorrhagia and anemia.

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

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