ORIGINAL ARTICLE: GYNECOLOGY AND MENOPAUSE

Efficacy and safety of repeated use of ulipristal acetate in uterine fibroids

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Objective: To investigate the efficacy and safety of repeated 12-week courses of 5 or 10 mg daily of ulipristal acetate for intermittent treatment of symptomatic uterine fibroids.
Design: Double-blind, randomized administration of two 12-week courses of ulipristal acetate.
Setting: Gynecology centers.
Patient(s): A total of 451 patients with symptomatic uterine fibroid(s) and heavy bleeding.
Intervention(s): Two repeated 12-week treatment courses of daily 5 or 10 mg of ulipristal acetate.
Main Outcome Measure(s): Amenorrhea, controlled bleeding, fibroid volume, quality of life (QoL), pain.
Result(s): In the 5- and 10-mg treatment groups (62% and 73% of patients, respectively) achieved amenorrhea during both treatment courses. Proportions of patients achieving controlled bleeding during two treatment courses were >80%. Menstruation resumed after each treatment course and was diminished compared with baseline. After the second treatment course, median reductions from baseline in fibroid volume were 54% and 58% for the patients receiving 5 and 10 mg of ulipristal acetate, respectively. Pain and QoL improved in both groups. Ulipristal acetate was well tolerated with less than 5% of patients discontinuing treatment due to adverse events.

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Conclusion(s): Repeated 12-week courses of daily oral ulipristal acetate (5 and 10 mg) effectively control bleeding and pain, reduce fibroid volume, and restore QoL in patients with symptomatic fibroids.
Clinical Trial Registration Number: NCT01629563 (PEARL IV). (Fertil Steril® 2015;■: ■–■. ©2015 by American Society for Reproductive Medicine.)
Key Words: Repeated intermittent use, ulipristal acetate, uterine fibroid, quality of life, long-term treatment

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Uterine leiomyomas, or fibroids, occur in 20%–40% of women of reproductive age (1). The most common symptoms are heavy menstrual bleeding, pain, dysmenorrhea, pelvic pressure, and anemia, resulting in chronic fatigue that adversely affects the women's quality of life and fertility (2).

Surgical and other invasive interventions still dominate treatment (3). Medical therapy is currently limited to preoperative reduction of symptoms related to uterine bleeding and fibroid size (4, 5) with no medical therapy providing long-term efficacy and acceptable tolerability and safety (4–11).

Ulipristal acetate (5 mg) once daily dose is approved in Europe and Canada for preoperative fibroid treatment (12). Ulipristal acetate, a selective P receptor (PR) modulator with pharmacokinetic properties supporting once daily dosing (13) potently modulates PR activity without suppressing E_2 to postmenopausal levels, and shows proapoptotic/antiproliferative effects on fibroid cells (13–17). Several short-term (3 months) randomized clinical studies showed that ulipristal acetate effectively controls bleeding and shrinks fibroids (18–21). After treatment cessation, return of menstruation usually occurs within 4–5 weeks but fibroid volume reduction can be sustained for up to 6 months. In addition, treatment with ulipristal acetate improved quality of life, reduced fibroid-associated pain, and revealed no safety concerns (20, 21). A selective PR modulator administration has been shown in clinical studies to lead to a pattern of benign, nonphysiological, nonproliferative, histologic features of the endometrium termed Progesterone receptor modulator Associated Endometrial Changes (PAEC) (22–25). These changes spontaneously reverse a few weeks to months after the end of ulipristal acetate treatment (20, 21, 26). Hence, intermittent courses of 12-week ulipristal acetate treatment with off-treatment intervals are a potential option for the long-term medical management of fibroids (12). Another open-label clinical study indicated that repeated use of ulipristal acetate (10 mg/d) for four 12-week consecutive treatment courses could achieve control of uterine bleeding and pain, fibroid volume reduction, and restore quality of life (26). The study design allowed for subjects to choose whether to complete only one treatment course before surgery or to continue, leading to a substantial reduction in patient numbers between the first and second treatment courses.

We conducted the study PGL4001 (ulipristal acetate) Efficacy Assessment in Reduction of symptoms due to uterine Leiomyomata (PEARL IV) to evaluate the efficacy and safety of repeated 12-week courses of daily 5- or 10-mg doses of ulipristal acetate.

The primary null hypothesis for this study was that there would be no difference in the percentage of subjects who were in amenorrhea at the end of both treatment courses 1 and 2 for 10 mg of ulipristal acetate compared with 5 mg of ulipristal acetate.

MATERIALS AND METHODS

Study Design and Oversight

PEARL IV was a Phase III multicenter, randomized, double-blind, parallel group, long-term study investigating the efficacy and safety of 5 and 10 mg doses of ulipristal acetate for the treatment of uterine fibroids. PEARL IV was conducted in 46 study sites across 11 countries from June 2012 to February 2014. 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 study was designed by the sponsor (PregLem) with the involvement of academic investigators and a study statistician. Data were collected by an independent contract research organization (ICON Clinical Research), and handled and analyzed by an independent data management organization (CROS NT). Jacques Donnez vouches for the data accuracy and analysis, and the fidelity of the study to the protocol. We present the results of part I on the first two treatment courses.

Study Population

We enrolled premenopausal women with at least one fibroid $\geq$3 cm in diameter and none >12 cm, as assessed by ultrasonography. Heavy menstrual bleeding (pictorial blood-loss assessment chart [PBAC]) score >100 and uterine size <16 weeks of gestation were calculated. Eligible women were aged between 18 and 50 years inclusive, with a body mass index (BMI) of 18–40 (kg/m^2) and regular menstrual cycles of 22–35 days with FSH $\leq$20 IU/L. Written informed consent was obtained from all women. The main exclusion criteria are listed in Supplemental Table 1 in the Appendix (available online).

Randomization and Intervention

Women were allocated randomly by a web-integrated voice response system in a 1:1 ratio to receive either 5 or

10 mg/d of oral ulipristal acetate and matching placebos for two 12-week courses. Ulipristal acetate was started during the first 4 days of menstruation. Treatment courses were separated by a drug-free interval. The second course was commenced with the second off-treatment menstruation. After the second treatment course and subsequent menstruation, an end of part I visit was performed. The sequence of visits, treatments and biopsies illustrated in Appendix, Supplemental Figure 1 and Supplemental Table 2 (available online).

Assessment of Uterine Bleeding

Patients recorded their bleeding pattern in a diary using an 8-day PBAC (27, 28) at screening and during the first menstruation after each treatment course. A PBAC score of >100 indicates menorrhagia. Bleeding pattern outside of the time frame was recorded in a diary with a simplified semiquantitative questionnaire containing four categories defined as "no bleeding," "spotting," "bleeding," or "heavy bleeding." Patients were asked to record their bleeding daily from start of treatment to the end of the observation visit.

Assessment of Endometrial Histology

Endometrial biopsies were obtained at screening and after treatment course 2 (10–18 days after start of menses for both treatment courses). An additional biopsy was performed during treatment course 1 if the screening biopsy was inadequate. All biopsies were assessed by three independent pathologists blinded to visit sequence, study group assignment, and each other's assessments.

Assessment of Fibroid Size and Endometrial Thickness

Fibroid and endometrial thickness measurements were carried out by transvaginal ultrasound at screening, post-treatment course 1 (10–18 days after start of menses), at the end of treatment course 2, and after treatment course 2 (10–18 days after start of menses for both treatment courses).

End Points

The primary efficacy end point was the percentage of patients in amenorrhea at the end of both treatment courses. Amenorrhea was defined as no more than 1 day of spotting within a 35-day interval.

Secondary efficacy end points included amenorrhea at the end of each treatment course and the last 56 days of each treatment course, controlled bleeding at the end of both courses and each treatment course individually (defined as no episodes of heavy bleeding and a maximum of 8 days of bleeding during the last 56 days of a treatment course), time to amenorrhea at the start of each individual treatment course, volume of three largest fibroids, and uterus (measured by transvaginal ultrasound), pain, and quality of life.

The safety end points included number and proportion of patients withdrawing from treatment early for safety reasons, number and proportion of patients experiencing adverse events including clinically significant changes in gynecological or breast examination, ovarian ultrasound, electrocardiogram, laboratory parameters, vital signs, and endometrial histology.

Statistical Analysis

Efficacy analyses were based on the full analysis set, defined as all randomized and treated patients. All statistical tests were two-sided, with a 5% level of significance. No adjustments were made for the multiple testing of secondary end points. In general, missing values were not imputed before analysis. However, if 3 consecutive days or less of the daily bleeding pattern were missing, the missing values were imputed with the greatest strength of bleeding immediately before or after the period of missing days.

The results for binary end points (including the primary efficacy end point) for 10 mg of ulipristal acetate versus 5 mg of ulipristal acetate were compared using χ^2 tests, with confidence intervals of the difference calculated using the Newcombe-Wilson score method (29). The change in total fibroid volume and uterine volume were analyzed by repeated-measures analysis of covariance after a log-transformation, with the results back-transformed before presentation. The change from baseline in PBAC scores was analyzed by the Wilcoxon rank sum test with the Hodges-Lehmann estimator (and corresponding Moses confidence interval) used for the differences in medians (30).

Assuming a dropout rate of approximately 10%, we estimated that 444 patients should be randomized for the study to have a power more than 85% to detect an absolute difference in the primary end point of 14% or more.

RESULTS

Patients

Demographic and baseline characteristics were balanced among the two treatment groups (Table 1). All patients had moderate-to-severe bleeding, and many had considerable pain, as well as impaired quality of life (Table 1). More than 90% patients completed both treatment courses. Adverse events (21 patients) and lack of efficacy (3 patients) were infrequent causes of study discontinuation (Appendix and Supplemental Fig. 2, available online).

Efficacy

Menstrual bleeding. In the 5- and 10-mg treatment groups (62% and 73% patients, respectively) achieved amenorrhea at the end of both treatment courses ($P=.03$; Table 2). Rates of amenorrhea after each individual treatment course were higher for patients receiving 10 mg (~83%) than 5 mg (72%–74%) (Supplemental Table 3 in the Appendix, available online) The median times to amenorrhea after the start of each treatment course were ≤6 days for each treatment group (Table 2). The proportions of patients with controlled bleeding at the end of both treatment courses were >80%, with no statistically significant differences between treatment groups (Table 2).

Menstruation resumed in most patients after the end of each treatment course within a median time of ≤28 days.

TABLE 1

Baseline characteristics (full analysis set).

Characteristic	Ulipristal acetate 5 mg (N = 228)	Ulipristal acetate 10 mg (N = 223)
Age (y), mean (SD)	41.6 (5.4)	41.1 (5.1)
Ethnicity, n (%)		
Caucasian	211 (92.5)	214 (96.0)
Black	12 (5.3)	8 (3.6)
Other	4 (1.8)	1 (0.4)
Not reported	1 (0.4)	0
Weight (kg), mean (SD)	69.2 (12.7)	70.0 (12.8)
BMI (kg/m^2), mean (SD)	25.2 (4.1)	25.3 (4.5)
PBAC Score, median (IQR)	224 (148–357)	215 (151–373)
Total volume of three largest fibroids (cm^3), median (IQR)	42.6 (24.0–94.2)	43.6 (27.3–117.3)
Uterine volume (cm^3), median (IQR)	176.9 (113.1–269.8)	175.22 (116.6–267.6)
Pain assessment (VAS), median (IQR)	39.5 (15.3–62.6)	43.0 (18.5–67.5)
UFS-QoL questionnaire		
Symptom severity, median (IQR)	50.0 (37.5–62.5)	50.0 (37.5–62.5)
HRQL, median (IQR)	56.9 (42.2–75.9)	55.2 (41.4–71.6)

Note: BMI = body mass index; HRQL = health-related quality of life; IQR = interquartile range; SD = standard deviation; UFS-QoL = uterine fibroid symptom and health-related quality of life questionnaire; VAS = visual analogue scale (score range, 0–100, the higher the greater pain).

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Off-treatment menstrual bleeding (PBAC days 1–8, Appendix and Supplemental Figure 3) progressively reduced from medians of >200 at the start of the first course to <100 after the end of the second ulipristal acetate course in both treatment groups (Table 2).

Fibroid volume. The median reductions in the combined volume of the three largest fibroids from baseline to the period after the first menses at the end of treatment course 1 were 38% and 38%, and for treatment course 2, 54% and 58% for patients receiving 5 and 10 mg of ulipristal acetate, respectively (Table 2).

Pain and quality of life. Median visual analogue scale pain scores for patients receiving 5 and 10 mg of ulipristal acetate decreased substantially from baselines of 39.5 and 43.0, respectively, to 6.0 (both treatment groups) at the end of course 1 (Fig. 1A). There was some relative return of pain when menstruation resumed during the off-treatment period (median scores, 22.5 and 22.0) before decreasing again to medians of 6.0 and 5.0 at the end of the second treatment course for patients receiving 5 and 10 mg, respectively. Quality of life was severely impaired at baseline (Fig. 1B and C), but was substantially improved at the end of both treatment courses for treatment groups. As with pain there was a partial deterioration of quality of life during the off-treatment period between treatment courses.

Surgery. Surgery was performed in only three and five patients receiving 5 and 10 mg of ulipristal acetate, respectively (Appendix, available online).

General safety. The proportion of patients with adverse events during the first treatment course was the same (44%) for both treatment groups (Table 3). Fewer patients reported adverse events during the second treatment course (27% and 30% for the 5- and 10-mg treatment groups, respectively). Headaches and hot flushes were the most frequently reported adverse events, but occurred in ≤10% of patients, and only one event of headache was reported as severe. Overall 21 (<5%) patients discontinued treatment at any time during or after the two treatment courses due to adverse events. There were 18 serious adverse events reported during part I, 9 occurring during treatment and 9 occurring between or after treatment courses (Table 3). The investigators assessed only five serious adverse events (4 cases of menorrhagia and a partial expulsion of a leiomyoma) as possibly related to ulipristal acetate therapy. No safety concerns were identified from physical examination, vital signs, laboratory safety tests, ovarian ultrasound, and electrocardiograms.

Endometrial safety. Transient increases in endometrial thickness, assessed by transvaginal ultrasound, occurred in less than 10% patients after each ulipristal acetate course (Supplemental Table 4 in the Appendix, available online). Some nonphysiological features, compatible with PAEC, were reported by at least two pathologists for 17 biopsies (8%) at screening in each treatment group, and for 29 (16%) and 35 biopsies (19%) after treatment course 2 for the 5- and 10-mg treatment groups, respectively (Supplemental Table 3 in the Appendix). Three cases of hyperplasia were also reported, including one simple atypical endometrial hyperplasia that resolved into "benign secretory endometrium" by the end of treatment. The after treatment biopsy sample from another patient was reported as endometrial adenocarcinoma by one of the three pathologists; however, adenocarcinoma was already observed by the same pathologist at the initial biopsy (Table 3 and Appendix [available online]).

Laboratory Parameters

Laboratory results did not reveal any safety signals and no patients discontinued treatment due to test abnormalities. A table detailing the laboratory results can be found in Supplemental Table 5 in the Appendix (available online).

DISCUSSION

The potential of long-term selective PR modulator treatment to control bleeding, progressively shrink fibroids, and enable patients to avoid surgery was unknown. Due to uncertainty

TABLE 2

Key efficacy outcomes (full analysis set).

Variable	Ulipristal acetate 5 mg (N = 228)	Ulipristal acetate 10 mg (N = 223)	Difference (95% CI) (ulipristal acetate 10 mg vs. 5 mg)	*P* value
Primary end point				
Amenorrhea at the end of both treatment courses (1 and 2), no./total no. (%)	122/197 (61.9)	136/187 (72.7)	10.8 (1.5–20.1)	.03
Secondary end points				
Controlled bleeding[a] at the end of both treatment courses (1 and 2), no./total no. (%)	150/185 (81.1)	148/172 (86.0)	5.0 (−2.7 to 12.6)	.26
Time to amenorrhea in course 1 (d), median (IQR)	5 (2–9)	4 (2–7)		
Time to amenorrhea in course 2 (d), median (IQR)	5 (4–9)	6 (4–8)		
PBAC (baseline actual), median (IQR)	224 (148–357) (N = 218)	215 (151–373) (N = 214)		
After treatment course 1, median (IQR)	123 (45–313) (N = 172)	129 (56–285) (N = 156)		
After treatment course 1 (CFB), median (IQR)	−87 (−167 to 13) (N = 167)	−85 (−209 to −12) (N = 151)	−13 (−54 to 28)	.55
After treatment course 2, median (IQR)	92 (44–243) (N = 159)	99 (37–202) (N = 152)		
After treatment course 2 (CFB), median (IQR)	−95 (−216 to 9) (N = 152)	−110 (−236 to −50) (N = 146)	−28 (−65 to 6)	.10
Total volume of three largest fibroids (cm^3), baseline actual, median (IQR)	42.6 (24.0–94.2)	43.6 (27.3–117.3)		
After first menses after treatment course 1 (%CFB), median (IQR)	−38.0 (−60.3 to −14.3) (N = 207)	−58.1 (−77.0 to −32.9) (N = 192)	0.91 (0.80–1.03)[b]	.15
End of treatment course 2 (%CFB), median (IQR)	−54.1 (−74.6 to −33.0) (N = 197)	−58.0 (−74.1 to −36.3) (N = 200)	0.89 (0.75–1.07)[b]	.21
After first menses after treatment course 2 (%CFB), median (IQR)	−53.8 (−77.1 to −23.4) (N = 188)	−58.09 (−77.0 to −32.9) (N = 192)	0.83 (0.69–1.01)[b]	.06
Fibroid volume reduction ≥25%				
After first menses after treatment course 1, no./total no. (%)	129/207 (62.3)	137/206 (66.5)	4.2 (−5.0 to 13.4)	.43
End of treatment course 2, no./total no. (%)	158/197 (80.2)	166/200 (83.0)	2.8 (−4.8 to 10.4)	.56
After first menses after treatment course 2, no./total no. (%)	139/188 (73.9)	152/192 (79.2)	5.2 (−3.3 to 13.7)	.28
Uterine volume (cm^3), baseline actual, median (IQR)	176.9 (113.1–269.8)	175.2 (116.6–267.6)		
After first menses after treatment course 1 (%CFB), median (IQR)	−13.3 (−28.5 to 8.2) (N = 214)	−13.0 (−29.5 to 3.5) (N = 211)	0.99 (0.92–1.05)[b]	.67
End of treatment course 2 (%CFB), median (IQR)	−23.6 (−40.9 to −4.4) (N = 205)	−25.5 (−44.7 to −5.9) (N = 203)	0.96 (0.88–1.04)[b]	.32
After first menses after treatment course 2 (%CFB), median (IQR)	−20.38 (−35.1 to 2.6) (N = 194)	−21.9 (−41.5 to 0.4) (N = 196)	0.95 (0.88–1.03)[b]	.24
Uterine volume reduction ≥25%				
After first menses after treatment course 1, no./total no. (%)	63/214 (29.4)	66/211 (31.3)	1.8 (−6.9 to 10.6)	.76
End of treatment course 2, no./total no. (%)	98/205 (47.8)	103/203 (50.7)	2.9 (−6.8 to 12.6)	.62
After first menses after treatment course 2, no./total no. (%)	90/194 (46.4)	90/196 (45.9)	−0.5 (−10.4 to 9.4)	1.00

Note: If a woman had more than three consecutive missing days in the last 35 d of a treatment course the amenorrhea assessment was left as missing, unless the women had reported bleeding during these last 35 d (subject is not in amenorrhea). Sensitivity analyses for end point are reported in the Appendix, available online. %CFB = percent change from baseline; CFB = change from baseline; CI = confidence interval; IQR = interquartile range; PBAC = pictorial blood-loss assessment chart.

[a] Controlled bleeding was defined as no episodes of heavy bleeding and a maximum of 8 d of bleeding during the last 56 d of a course of treatment.

[b] Ratio of ulipristal acetate 10 mg ratio to baseline to ulipristal acetate 5 mg ratio to baseline (95% CI).

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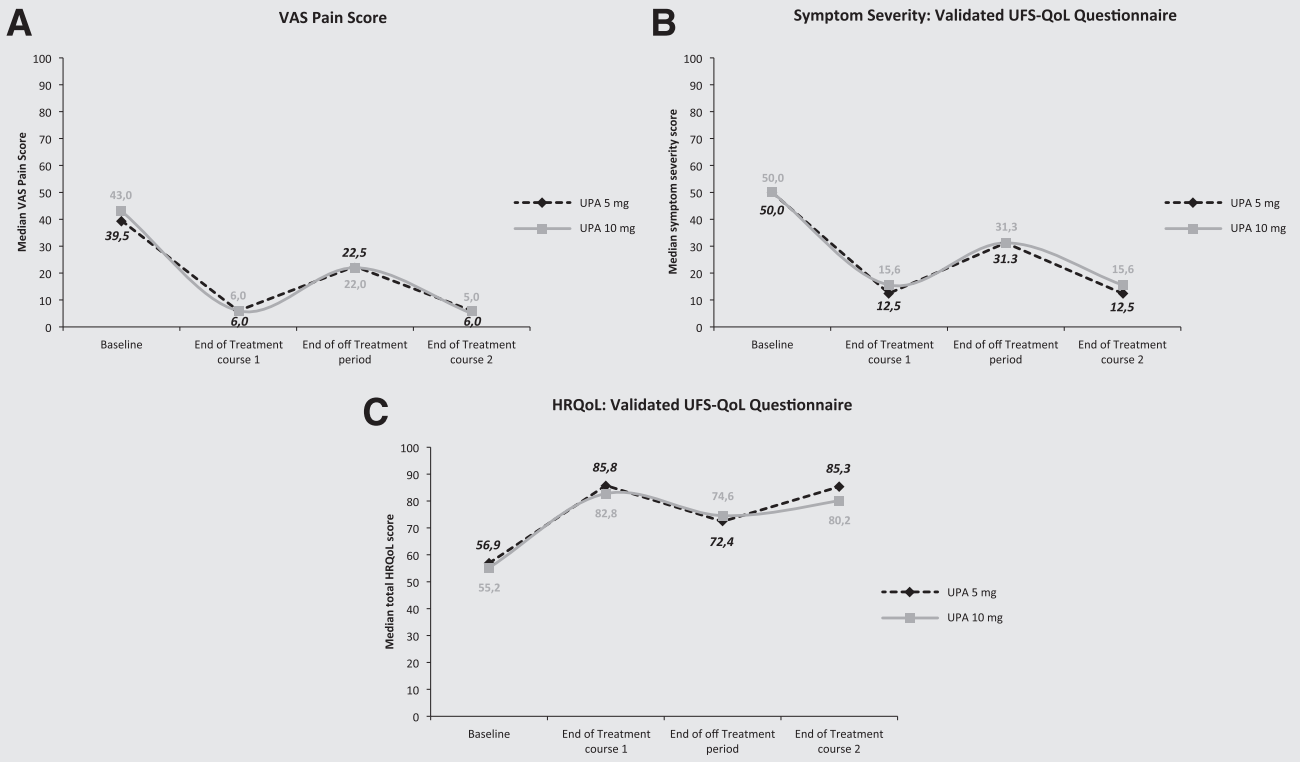
FIGURE 1



Effect of ulipristal acetate (UPA) on (**A**) pain, (**B**) symptom severity, and (**C**) health-related quality of life (QoL). (**A**) shows the fibroid related pain using a visual analogue scale (VAS) ranging from 0 (no pain) to 100 (worst possible pain). (**B**) shows the uterine fibroid symptom severity consisting of a validated questionnaire where lower scores indicate fewer symptoms. The symptom severity score comprises four domains: bleeding, abdominal pressure, urination frequency, and fatigue. A level of 23 has been reported in a uterine fibroid symptom and health-related quality of life questionnaire (UFS-QoL) study for healthy subjects (34). (**C**) shows the health-related (HR) QoL where higher scores indicate a better QoL and includes six domains: concern, activities, energy/mood, control, self consciousness, and sexual function. A level of 86 has been reported in a UFS-QoL validation study as a reference for healthy subjects (34).

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as to whether continuous selective PR modulator treatment could lead to adverse consequence for the endometrium, a model of intermittent treatment courses has been adopted. In this randomized, double-blind study, we administered two 12-week courses of ulipristal acetate (5 or 10 mg/d) to patients with fibroids and severe bleeding and evaluated the efficacy and safety during a period of about 10 months. Baseline fibroid volume and bleeding severity in the recruited patients were similar to those reported for other clinical studies (20, 21, 26). More than 90% of patients in each group completed both ulipristal acetate treatment courses, leading to a high level of confidence in interpretation of the results.

Both dose regimens of ulipristal acetate controlled the most debilitating symptom of fibroids (menorrhagia) as evidenced by the high proportion of patients with amenorrhea at the end of each treatment course. Rates of amenorrhea were approximately 10% more for the 10-mg dose compared with the 5-mg dose regimen, but even with the 5-mg dose more than 80% patients achieved controlled bleeding at the end of both treatment courses. This leads us to conclude that the 5-mg dose approved for preoperative use should be considered for future long-term symptom management. As expected, menstruation resumed after each treatment course but the magnitude of menstrual bleeding progressively diminished during the off-treatment periods to a median level below the threshold for menorrhagia.

Both doses of ulipristal acetate were effective in shrinking fibroids, more than halving the fibroid volume in more than 50% of patients by the end of the second treatment course. Patients also reported substantial improvements in pain and quality of life during treatment, and these improvements were partly maintained during the off-treatment period. Very few patients (<2%) discontinued the study to undergo surgery.

Most adverse events were mild or moderate and occurred less frequently in the second treatment course. Four serious adverse events considered related to ulipristal acetate by the investigator were cases of menorrhagia (all occurring off-treatment when menstruation was expected to resume). This incidence is not more than reported in previous studies of ulipristal acetate, placebo, and comparator agents in women with fibroid-related menorrhagia (20, 21, 26). The only other serious adverse event considered related to ulipristal acetate was a partial expulsion of a leiomyoma.

TABLE 3

Adverse events (safety set).

	Treatment course 1				Treatment course 2			
	ulipristal acetate 5 mg (N = 230)		ulipristal acetate 10 mg (N = 221)		ulipristal acetate 5 mg (N = 215)		ulipristal acetate 10 mg (N = 205)	
Type	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
On-treatment AE leading to study withdrawal[a]	6	2.6	7	3.2	1	0.5	4	2.0
Off-treatment AE leading to study withdrawal[b]	2	0.9	1	0.5	0	0	0	0
At least one on-treatment AE[a]	102	44.3	98	44.3	59	27.4	61	29.8
Headache	21	9.1	23	10.4	13	6.0	5	2.4
Hot flush	13	5.7	15	6.8	8	3.7	6	2.9
Breast pain/tenderness/discomfort	7	3.0	5	2.3	2	0.9	0	0
Influenza	9	3.9	8	3.6	0	0	1	0.5
Nasopharyngitis	2	0.9	8	3.6	3	1.4	1	0.5
Nausea	8	3.5	4	1.8	0	0	0	0
Fatigue	3	1.3	7	3.2	3	1.4	2	1.0
At least one off-treatment AE[b]	37	16.1	42	19.0	25	11.6	22	10.7
Headache	6	2.6	8	3.6	1	0.5	2	1.0
At least one on-treatment SAE[a]	3	1.3	3	1.4	1	0.5	2	1.0
Anemia	1	0.4	0	0	0	0	0	0
Arteriospasm coronary	0	0	1	0.5	0	0	0	0
Tinnitus	0	0	1	0.5	0	0	0	0
Cholelithiasis	0	0	1	0.5	0	0	0	0
Periarthritis	1	0.4	0	0	0	0	0	0
Bipolar disorder (same subject)	1	0.4	0	0	1	0.5	0	0
Breast cancer	0	0	0	0	0	0	1	0.5
Menorrhagia	0	0	0	0	0	0	1	0.5
At least one off-treatment SAE[b]	5	2.2	3	1.4	1	0.5	0	0
Menorrhagia	4	1.7	0	0	0	0	0	0
Castleman's disease	1	0.4	0	0	0	0	0	0
Partial expulsion of uterine myoma	0	0	1	0.5	0	0	0	0
Small intestinal obstruction	0	0	1	0.5	0	0	0	0
Carpal tunnel syndrome	0	0	1	0.5	0	0	0	0
Endometrial adenocarcinoma[c]	0	0	0	0	1	0.5	0	0

Note: Table includes adverse events (AEs) occurring in ≥3% patients as well as all serious adverse events (SEA) occurring at or after the first dose of study drug and on or before the last visit after treatment course 2. Patients could have more than one AE of same type.

[a] On-treatment Treatment Emergent Adverse Events (TEAEs) are defined as events whose start date is during or after the first dose of study drug, up to and including 7 days after the last dose of study medication within each treatment course.

[b] Off-treatment TEAEs are defined as events whose start date is more than 7 d after the last dose of study medication within each treatment course and before the start of the next treatment course.

[c] Preexisting condition: On initial and follow-up biopsy, one of three pathologists reported presence of adenocarcinoma. Further details the Appendix, available online.

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Donnez et al. (20, 21) previously reported that a 3-month course of ulipristal acetate induces PAEC in approximately 60% of patients and that this is fully reversible 6 months after the end of treatment. In the present study the endometrium was biopsied approximately 6 weeks after the end of the second course of ulipristal acetate, and nonphysiological features were observed in approximately 16% and 19% patients who had been treated with 5 and 10 mg of ulipristal acetate, respectively. Thus repeated courses of ulipristal acetate do not increase the frequency of PAEC. The incidence of endometrial hyperplasia after two treatment courses was <1%, which is consistent with the expected frequency in women with abnormal uterus bleeding within this age range (31).

Currently there are no approved long-term medical treatment options for the management of patients with symptomatic fibroids. The GnRH agonists with hormonal add-back therapy (9, 32, 33, 35, 36), oral progestins (alone), and intrauterine levonorgestrel (37–41) have been used but are associated with various tolerability and safety issues and inconsistent or lack of efficacy in shrinking fibroids. To be acceptable as a long-term management option, medical therapy should rapidly control bleeding and progressively shrink the fibroids, in addition to showing a good safety profile. If medical treatment has to be intermittent, then the regimen must be simple, and there should not be regrowth of fibroids and return of symptoms during off-treatment periods. We believe that the intermittent 12-week ulipristal acetate daily dose regimens (the first course to be administered at the start of a menstrual cycle, and subsequent courses to commence at the start of the second menses after the previous course) fulfill most of these criteria, as evidenced by the low side effect burden and discontinuation rate, and the high compliance with treatment. Some patients did experience pain and excessive bleeding during off-treatment periods but generally not of the same magnitude as prior to treatment. Also there was no regrowth of fibroids observed during follow-up. Thus our results suggest that intermittent ulipristal acetate is a viable and attractive long-term medical management option for patients with symptomatic fibroids. Our data are also consistent with the results of an earlier study (21) reporting that up to four intermittent treatment courses of ulipristal acetate could be successively administered to control

bleeding and shrink fibroids. However, interpretation of the results of that study was limited by the open-label design with only one dose (10 mg not currently approved), the limited sample size, and by the inclusion of subjects desiring only a single course of treatment before surgery, leading to a substantial decrease in numbers of patients progressing to the second treatment course.

There are some weaknesses in our study. We could not use a placebo control for long-term ulipristal acetate treatment. However, we previously demonstrated that a 3-month course of ulipristal acetate was superior to placebo and not inferior to a GnRH agonist for control of uterine bleeding (21–26). Although our study showed an advantage of the 10-mg dose for rates of amenorrhea, bleeding control was comparable with the 5-mg dose.

We report results for only two treatment courses, but further intermittent treatment courses have been reported as effective (21). We did not recruit many women of African origin, but previous short-term studies have reported efficacy in these patients (18, 19).

In conclusion, in this large double-blind, randomized study, we showed that repeated 12-week courses of oral ulipristal acetate (5 and 10 mg/d) effectively and safely control bleeding and pain, reduce fibroid volume, and restore quality of life in patients with symptomatic fibroids. Compliance with intermittent treatment is good, and symptomatic improvement and fibroid volume shrinkage can be largely maintained during the off-treatment periods.

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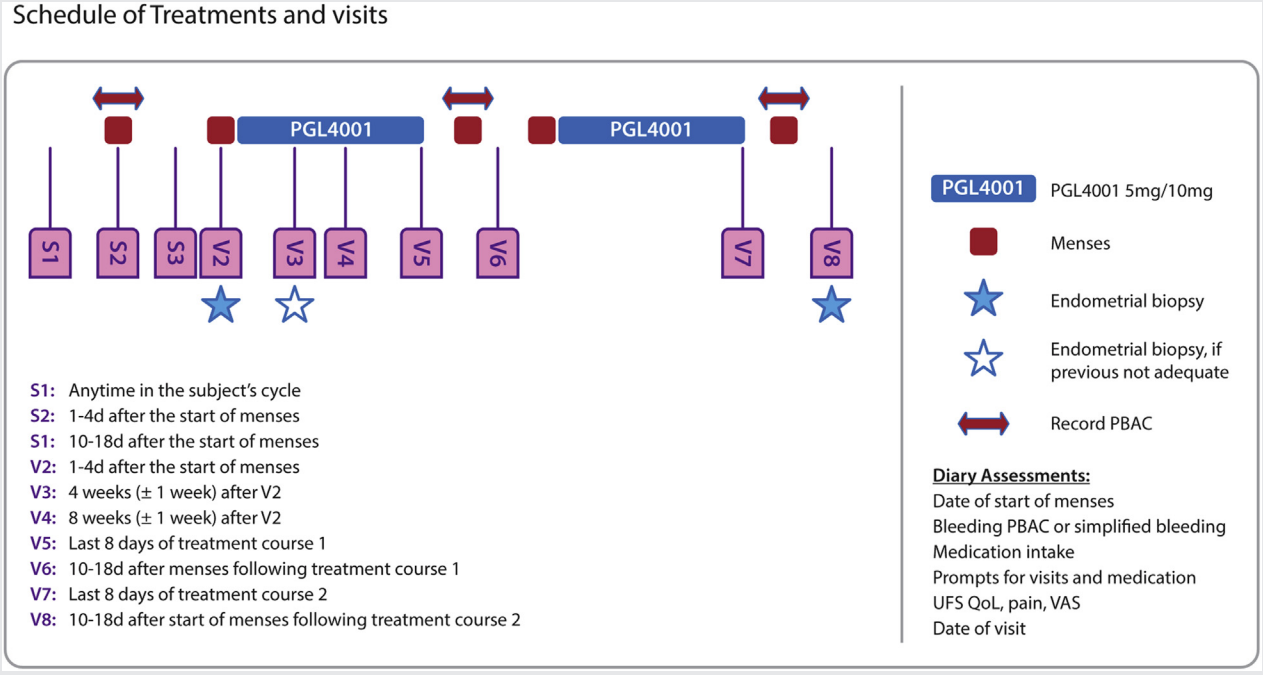
SUPPLEMENTAL FIGURE 1



Schedule of treatments and visits.

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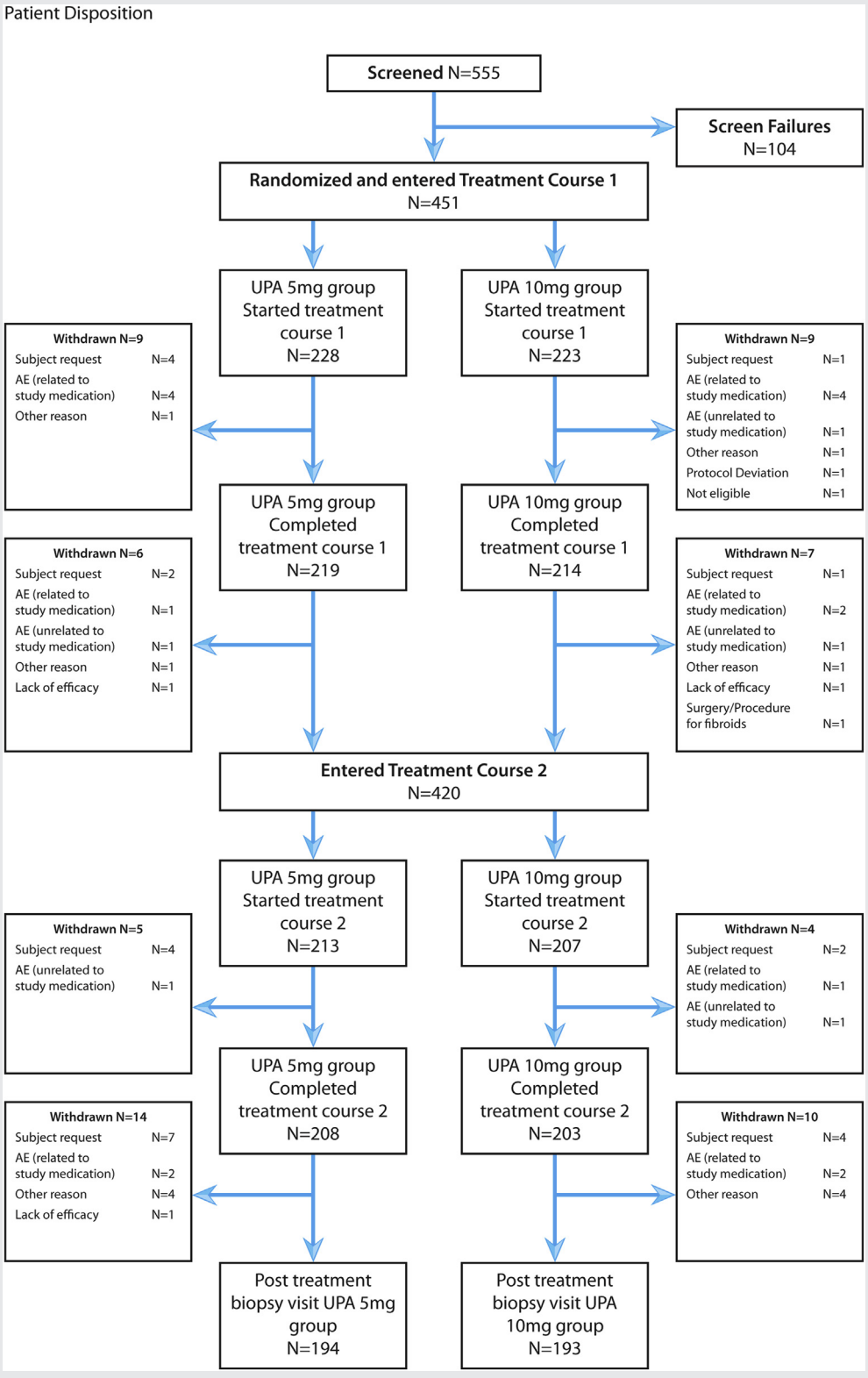
SUPPLEMENTAL FIGURE 2



Patient disposition. Withdrawals are presented according to the timeframes in which they occurred, either during treatment or after treatment completion for each course. Two subjects randomized to the ulipristal acetate 10 mg group received ulipristal acetate 5 mg treatment in error; these subjects are included in the FAS Sets according to randomization, and in the Safety Set according to treatment received.

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SUPPLEMENTAL FIGURE 3

Pictorial Bleeding Assessment Chart recording document

Day 1 of Menstruation:

D D M M M 2 0 Y Y Y Y

Score	Towels	1	2	3	4	5	6	7
			No bleeding ☐	No bleeding ☐	No bleeding ☐	No bleeding ☐	No bleeding ☐	No bleeding ☐
1								
5								
20								
	Tampons							
1								
5								
10								
1	Small Clots / Flooding							
5	Large Clots / Flooding							

Pictoral Bleeding Assessment Chart recording document. PBAC is one of the current standard methods used to objectively estimate menstrual blood loss and diagnose menorrhagia. The method which was developed and validated by Higham and Janssen defines excessive bleeding as a PBAC score >100.

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