ORIGINAL ARTICLE: GYNECOLOGY AND MENOPAUSE

Long-term medical management of uterine fibroids with ulipristal acetate

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Objective: To investigate the efficacy and safety of repeated 12-week courses of 5 or 10 mg daily ulipristal acetate for intermittent treatment of symptomatic uterine fibroids.

Design: Double-blind, randomized administration of four 12-week courses of ulipristal acetate.

Setting: Gynecology centers.

Patient(s): Four hundred fifty-one subjects with symptomatic uterine fibroid(s) and heavy menstrual bleeding.

Intervention(s): Four repeated 12-week treatment courses of daily 5 or 10 mg ulipristal acetate.

Main Outcome Measure(s): Endometrial safety and general safety, laboratory parameters, amenorrhea, controlled bleeding, fibroid volume, quality of life (QoL), and pain.

Result(s): Efficacy results, such as bleeding control and fibroid volume reduction, were in line with previously published data. Pain and QoL showed marked improvements from screening, even during the off-treatment intervals. The safety profile of ulipristal acetate was confirmed, and repeated treatment courses did not increase the occurrence of adverse reactions. There were no significant changes in laboratory parameters during the study. The percentage of subjects with endometrial thickness ≥ 16 mm was 7.4% (all subjects) after the first treatment course and returned to below screening levels (4.9%) in subsequent treatment courses. As in previous studies, ulipristal acetate did not increase the occurrence of endometrial features of concern. The frequency of nonphysiological changes did not increase with repeated treatment. They were

observed in 17.8% and 13.3% of biopsies after treatment courses 2 and 4, respectively, and were reversible after treatment cessation.

Conclusion(s): The results of this study demonstrate the efficacy and further support the safety profile of repeated intermittent treatment of symptomatic fibroids with ulipristal acetate.

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Key Words: Ulipristal acetate, uterine fibroid, pain, bleeding, fibroid volume, long-term treatment

Uterine fibroids are benign smooth muscle tumors of the uterus (1). When symptomatic, they are frequently responsible for heavy menstrual bleeding (2), infertility (2), and a decreased quality of life (3) (QoL). Ulipristal acetate (UPA) is a possible option for medical therapy. UPA is a steroid compound with the main pharmacodynamic property of reversibly blocking the progesterone (P) receptor in its target tissue, acting as a potent orally active P receptor modulator. It belongs to the class of selective P receptor modulators (SPRMs).

UPA is indicated for intermittent and preoperative treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age.

In the two short-term phase III studies for European registration PEARL I (4) (comparator: placebo) and PEARL II (5) (active comparator: leuprolide acetate; a GnRH agonist authorized for preoperative treatment of fibroids), UPA was shown to be effective in controlling uterine bleeding related to myomas, to reduce myoma size, and to have a good safety profile. In clinical studies, SPRM administration has been associated with a pattern of benign, nonphysiological, nonproliferative, histologic features of the endometrium termed P receptor modulator associated endometrial changes (PAEC). These changes are characterized by cystic glandular dilatation, apoptosis, low mitotic activity in the glands and stroma, absence of stromal breakdown, and glandular crowding as clearly described by Williams et al. (6). The previous clinical studies illustrated the reversibility of PAEC on endometrial biopsies taken 6 months after UPA treatment completion.

Two additional studies were initiated to assess the efficacy and safety of long-term, repeated, intermittent administration of UPA in patients with symptomatic fibroids. PEARL III and its extension (7) (long-term, intermittent, 10 mg/day for 3 months with drug-free intervals) demonstrated that this dosing regimen provided an effective and well-tolerated treatment of the symptoms of uterine myomas with efficient bleeding control accompanied by a reduction in fibroid volume.

The PEARL IV study, reported here, was the second pivotal study to investigate the use of UPA for long-term intermittent use and the first one reporting results with the authorized dose of UPA 5 mg. The main objective was to assess the sustained efficacy and safety of up to four intermittent treatment courses with UPA 5 or 10 mg doses for uterine bleeding, myoma volume, pain, QoL, and safety. The results from the first two treatment courses have previously been published (8).

The primary null hypothesis was that there would be no difference in the percentage of subjects who are in amenorrhea at the end of all four treatment courses for UPA 10 mg compared with UPA 5 mg.

The data reported herein focus on the new findings from treatment courses 3 and 4 as well as the four treatment courses combined. With the recently registered indication of intermittent treatment with UPA, the absence of endometrial and laboratory safety findings associated with long-term therapy is of special interest to clinicians.

MATERIALS AND METHODS
Study Design and Oversight

The study design and oversight of the phase III double-blind, randomized PEARL IV study have previously been published (7). PEARL IV was conducted in 46 centers in 11 European countries from June 2012 to December 2014. The study was approved by the independent ethics committees 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 S.A.) with the involvement of academic investigators and a contract study statistician (CROS NT). Data were collected by an independent Contract Research Organization (ICON Clinical Research) and handled and analyzed by an independent Data Management organization (CROS NT). The first author vouches for the data accuracy and analysis and the fidelity of the study to the protocol.

Study Population

Subjects enrolled in the study were premenopausal women with at least one fibroid ≥3 cm in diameter and none >12 cm (as assessed by ultrasound), heavy menstrual bleeding >100 (pictorial blood-loss assessment chart [PBAC]), and uterine size <16 weeks of gestation. Eligible subjects were aged between 18 and 50 years inclusive, with body mass index 18–40 (kg/m^2) and regular menstrual cycles of 22–35 days with FSH ≤20 IU/L. Written informed consent

was obtained from all subjects. The main exclusion criteria are listed in Supplemental Table 1.

Randomization and Treatment

Subjects were allocated randomly by a web-integrated voice response system in a 1:1 ratio to receive either 5 or 10 mg of daily oral UPA and matching placebos for four 12-week courses. UPA was started during the first 4 days of menstruation. Treatment courses were separated by a drug-free interval. Subsequent courses started with the second menstruation in the off-treatment period. Final follow-up was performed after a 3-month drug-free period following the fourth treatment course.

The sequence of treatments and biopsies is illustrated in the Supplemental Figure 1.

Assessment of Uterine Bleeding

Subjects recorded their bleeding intensity in a diary using an 8-day PBAC (Supplemental Fig. 2) at screening and during the first menstruation after treatment courses 1, 2, and 4. A PBAC score >100 indicates menorrhagia. Outside this timeframe, bleeding was recorded using a simplified semiquantitative questionnaire containing four categories defined as "no bleeding", "spotting", "bleeding", or "heavy bleeding".

Assessment of Endometrial Histology

Endometrial biopsies were obtained at screening and post-treatment courses 2 and 4 and at 3 months post-treatment follow-up. Evaluation of all biopsies was performed by three independent pathologists who were blinded to visit sequence, study-group assignment, each other's assessments, and whether or not the subject had already received UPA treatment. The sample collection of endometrial tissue was performed by a gynecologist using a Pipelle de Cornier®. To allow collection of sufficient biopsy material, the biopsy was performed in the late proliferative or early secretory phase of the menstrual cycle (i.e., at least 10–18 days after the start of menstruation).

Assessment of Fibroid Size and Endometrial Thickness

Fibroid size and endometrial thickness measurements were carried out by transvaginal ultrasound at screening, at the end of treatment courses, and at follow-up. The ultrasonographer was blinded to the subject's treatment, and the same operator performed each subject's ultrasound assessments. At each visit, the three largest myomas and the endometrial thickness were measured. For consistent myoma volume evaluation, the ultrasonographer was requested to record the myomas in three dimensions as well as the type of myoma (submucosal, intramural, subserosal, pedunculated) and to photo-document the measurements.

Assessment of Pain and QoL

Pain and QoL assessments were carried out at screening, at the start and end of each treatment course, and at post-treatment follow-up. Pain was assessed using a visual analogue scale (VAS) ranging from 0 to 100, with higher scores indicating more severe pain. QoL was assessed using a validated questionnaire measuring uterine fibroid symptom severity (UFS-QoL), where lower scores indicate fewer symptoms and where a level of 23 has been reported for healthy subjects (3).

Endpoints

The primary efficacy endpoint for this study was the percentage of subjects in amenorrhea at the end of all four treatment courses, where amenorrhea was classified as no more than 1 day of spotting in a 35-day period.

Secondary efficacy endpoints included amenorrhea at the end of each individual treatment course (1, 2, 3, and 4); controlled bleeding in the last 56 days of each individual treatment course (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 during treatment courses 1, 2, 3, and 4; volume of three largest fibroids; and pain and QoL. The results for treatment courses 1 and 2 have previously been published (8).

The safety endpoints included the number and proportion of subjects withdrawing from treatment early for safety reasons and the number and proportion of subjects experiencing adverse events (AEs), including clinically significant changes in gynecological or breast examination, ovarian ultrasound, electrocardiogram (ECG), laboratory parameters, vital signs, and endometrial thickness and histology.

Statistical Analysis

Efficacy analyses were carried out on both the full analysis set (FAS) and the per protocol set (PP). The population of primary interest was the FAS, which was defined as all randomized and treated patients. The PP set was defined as all subjects who had completed all four treatment courses with no major deviation in any treatment course. All statistical tests were two-sided, with a 5% level of significance. No adjustments were made for the multiple testing of secondary endpoints. In general, missing values were not imputed before analysis. However, if only 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 endpoints (including the primary efficacy endpoint) for UPA 10 mg versus UPA 5 mg were compared using χ^2-tests, with confidence intervals of the difference calculated using the Newcombe-Wilson score method (9). The change in total fibroid volume and uterine volume was analyzed via 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 via the Wilcoxon rank-sum test with the Hodges-Lehmann estimator (and corresponding Moses confidence interval) used for the differences in medians (10).

ORIGINAL ARTICLE: GYNECOLOGY AND MENOPAUSE

Assuming a drop-out rate of approximately 10%, 444 subjects were to be randomized for the study to have >85% power to detect an absolute difference in the primary endpoint of ≥14%. This level of absolute difference was based on the results of the previous registration studies and was therefore of clinical relevance (5).

RESULTS
Patients

Demographic and baseline characteristics were comparable across the two treatment groups. All patients had moderate to severe bleeding, and many had considerable pain as well as impaired QoL (Supplemental Table 2). Seventy-five percent of patients completed all four treatment courses. Treatment compliance across both groups was high (≥80%), and the inter-treatment intervals were on average 51–56 days between each treatment course for both groups.

Efficacy

All efficacy results are presented for the FAS1 population, where subjects had to have started at least the first treatment course, unless other indicated. The percentages of subjects identified as being in amenorrhea for individual treatment courses 1, 2, 3, and 4 were 71.8%, 74.1%, 73.3%, and 69.6% in the 5 mg group and 82.6%, 82.2%, 78.3%, and 74.5% in the 10 mg group, respectively. A statistically significant difference was detected between the two treatment groups at

the end of course 1 (P=.011) but not at the end of treatment courses 2, 3, and 4 (Table 1 and Supplemental Table 3).

Of all subjects having started treatment, 48.7% in the 5 mg group and 60.5% in the 10 mg group were in amenorrhea in all four treatment courses (1, 2, 3, and 4 combined). A statistically significant difference was found between the two treatment groups (P=.027). To avoid the impact of dropouts, the same analysis was also performed on the FAS4, where subjects had to have started the fourth treatment course, and the PP set 4 (PP4), where subjects had to be at least 80% compliant in each of the four courses with no major protocol deviations. For FAS 4 and for PP4, the percentage of subjects assessed as being in amenorrhea at the end of all four treatment courses was 62.7% and 63.1% in the 5 mg and 72.1% and 73.2% in the 10 mg groups, respectively. No statistically significant difference was found between the two treatment groups for either of these populations (Table 1 and Supplemental Table 3).

The percentage of patients with controlled bleeding in the last 56 days for individual treatment courses ranged from 73.3% to 93.4% across both treatment groups, with corresponding median times to amenorrhea of 4–6 days in all groups for each treatment course. No statistically significant differences were detected between the two treatment groups at any of the time points (Table 1 and Supplemental Table 3).

PBAC was measured at screening and after courses 1, 2, and 4 to assess the level of menstrual bleeding. In the 5-mg group, the mean (median) levels at screening were 300.2 (224.0), and these decreased with each subsequent course to

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TABLE 1

Key efficacy outcomes (FAS 1 unless otherwise specified).

Variable	UPA 5 mg (n = 228)	UPA 10 mg (n = 223)	Difference (95% CI) (UPA 10 mg vs. UPA 5 mg)	P value
Primary endpoint: amenorrhea at the end of all four treatment courses, n/N (%)				
FAS 1[a]	95/195 (48.7)	112/185 (60.5)	11.8 (1.9–21.8)	.027
FAS 4[b]	94/150 (62.7)	106/147 (72.1)	9.4 (−1.2 to 20.0)	.107
PP set 4[c]	94/149 (63.1)	104/142 (73.2)	10.2 (−0.5 to 20.8)	.084
Secondary endpoints				
Controlled bleeding				
Controlled bleeding[d] at the end of all four treatment courses, n/N (%)	106/158 (67.1)	105/146 (71.9)	4.8 (−5.5 to 15.2)	.430
Controlled bleeding[d] at the end of treatment course 4, n/N (%)	148/202 (73.3)	144/192 (75.0)	1.7 (−6.9 to 10.4)	.781
PBAC				
PBAC scores, first menses postscreening, baseline actual, mean (median)	300.2 (224.0)	304.0 (214.5)	NA	NA
PBAC scores, first menses post-treatment course 4, mean (median)	139.7 (77.5)	128.2 (76.0)	−11.0 (−49.0 to 26.0)	.563
Total volume of three largest fibroids, cm³				
End of treatment course 4 %CFB, median (IQR)	−71.8 (−87.6 to −32.6)	−72.7 (−87.5 to −47.0)	0.88 (0.69–1.13)[e]	.314
Follow-up %CFB, median (IQR)	−65.0 (−85.1 to −28.4)	−67.4 (−87.4 to −44.6)	0.87 (0.67–1.14)[e]	.314
Fibroid volume reduction ≥25%: end of treatment course 4, n/N (%)	135/166 (81.3)	150/170 (88.2)	NA	NA

Note: If a woman had more than 3 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 this endpoint are reported in the Supplemental Material (available online). Results of additional time points and other secondary endpoints can be found in Supplemental Table 3. IQR = interquartile range; CFB = change from baseline; %CFB = percent change from baseline; NA = no formal statistical analysis.
[a] FAS 1 is defined as all subjects who received study treatment at least once for treatment course 1.
[b] FAS 4 is defined as all subjects who received study medication in the fourth treatment course at least once.
[c] PP set 4 is defined as all subjects who received study medication in the fourth treatment course for at least for 56 d.
[d] 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.
[e] Ratio of UPA 10 mg ratio to baseline to UPA 5 mg ratio to baseline (95% CI).

Donnez. Ulipristal acetate in uterine fibroids. Fertil Steril 2015.

levels of 139.7 (77.5) after course 4. The same pattern was also seen in the 10-mg group (screening, 304.0 [214.5]; after course 4, 128.2 [76.0]). No statistically significant differences were detected between the two treatment groups at any of the time points (Table 1 and Supplemental Table 3).

Clinically significant reduction of ≥ 25% volume of the three largest fibroids was reported after each treatment course. In both groups, the percentage of subjects with a clinically significant reduction increased from course 1 to course 4. In the 5-mg group, the percentages increased from 62.3% after course 1 to 78.1% after course 4. Similarly, in the 10-mg group, the percentages increased from 66.5% to 80.5%. (Table 1 and Supplemental Table 3). Further examination showed that at the end of four treatment courses, 73.5% of all subjects had a fibroid volume reduction of ≥ 25% and were in amenorrhea (Supplemental Fig. 4).

In addition, the percentage of subjects with a clinically significant volume reduction ≥ 50% increased from course 1 to course 4 in both treatment groups (Supplemental Table 3).

Pain scores improved in both groups during treatment; the median overall pain scores in the 5- and 10-mg groups at screening were 39 and 43, respectively, and ranged from 5 to 7 during treatment. Even during the off-treatment periods, including follow-up, the median pain ranged from 9.0 to 22.5. No statistically significant differences were detected between the two treatment groups at any of the time points (Supplemental Tables 4 and 5).

Similarly, median UFS-QoL symptom severity scores of 50 at screening corresponded well to published symptom severity scores for fibroid patients [3]. During treatment, median scores from 12.5 to 15.6 (which are scores comparable to those of healthy subjects [3]) indicated the important reduction of symptom severity in both groups. Even during the off-treatment periods, including follow-up, the median symptom severity score ranged from 18.8 to 31.3. No statistically significant differences were detected between the two treatment groups at any of the time points (Supplemental Tables 4 and 5).

Endometrial Safety

At screening for study eligibility, endometrial biopsies for a total of 493 subjects were reviewed by the central laboratory. Of these, nine (1.8%) subjects were not eligible for the study owing to abnormal findings (8 [1.6%] diagnoses of simple non-atypical hyperplasia and one diagnosis of complex non-atypical hyperplasia).

A consensus diagnosis (at least two out of three pathologists in agreement) of benign endometrium was reached by the independent pathologists for all subjects accepted into the study. Benign polyps were reported in seven (1.7%) subjects.

One subject from the 5-mg group had a diagnosis of complex atypical hyperplasia during the study. At follow-up and without any further medical or surgical intervention, this subject had a consensus diagnosis of benign endometrium. Four other subjects were reported to have benign polyps, and one subject from the 5-mg group was reported to have a hyperplasic polyp.

All cases of hyperplasia observed after treatment (including the cases previously reported [7]) returned to benign endometrium under continued treatment (four courses) and/or during the follow-up period. One case of hyperplasia was reported in the follow-up biopsy (3 months after treatment course 4). For this subject, all previous biopsies (including after treatment course 4) had been diagnosed as benign endometrium by the three independent pathologists.

The occurrence of nonphysiological endometrial changes was observed in 7.8% of the 5-mg group and 8.4% of the 10-mg group at screening. As expected, after treatment with UPA nonphysiological changes increased, but this increase was independent of the dose and the number of treatment courses. After treatment course 2, nonphysiological endometrial changes were observed in 16.3% and 19.2% of the biopsies for the 5- and 10-mg groups, respectively, decreasing to 16.2% and 10.3% after treatment course 4 (Table 2).

At follow-up, in 286 biopsies adequate for review, nonphysiological changes were observed in 9.0% and 6.3% of the biopsies for the 5- and 10-mg groups, respectively, which compares to the observed values at screening.

During the study, the median endometrial thickness remained between 7 and 8 mm. The percentage of subjects with endometrial thickness ≥ 16 mm was 7.4% (all subjects) after the first treatment course and returned to below screening levels (4.9%) in subsequent treatment courses. (Fig. 1 and Supplemental Table 3).

Laboratory Parameters

The median Hb value at screening was 12.55 and 12.40 g/dL for subjects from the 5- and 10-mg groups, respectively. From treatment course 1 to treatment course 4, Hb levels increased compared with screening values, reaching a peak at the end of treatment course 4, with median levels for the 5- and 10-mg groups of 13.10 and 13.35 g/dL, respectively (Supplemental Table 6).

The median Hct values at screening were 0.40 for both the 5- and 10-mg groups. During the study, Hct levels increased to reach a peak at the end of treatment course 2 for both treatment groups, median 0.42 (Supplemental Table 6).

E_2 levels remained stable in both treatment groups across the study period (Supplemental Table 6).

At screening, four (1.8%) and seven (3.2%), subjects had high values (>ULN, Upper Limit of Normal) for aspartate aminotransferase (AST) in the 5- and 10-mg groups, respectively. At the follow-up assessment, approximately 3 months after end of study treatment, four (2.4%) and six (3.6%) had high values in the two respective groups. For alanine aminotransferase (ALT), at screening four (1.8%) and two (0.9%) had high values, with two (1.2%) and four (2.4%) of patients also reporting high values at the follow-up assessment in the 5- and 10-mg groups, respectively. The number of subjects with high gamma glutamyl transferase (GGT) levels at screening were 14 (6.1%) and 10 (4.5%) for the 5- and 10-mg groups, respectively, with 12 (7.1%) and 15 (9.0%) also reporting high levels at follow-up (Supplemental Table 7).

For all lipid parameters, the levels for subjects from the 5- and 10-mg groups were comparable during the study. At

ORIGINAL ARTICLE: GYNECOLOGY AND MENOPAUSE

TABLE 2

Summary of endometrium biopsy results (safety population).

Treatment group	Category	Classification	Screening	After treatment 2	After treatment 4	Follow-up
				Visits		
UPA 5 mg (n = 230)	Endometrium biopsy performed	Yes	230	193	168	164
	Specimen adequate[a]	Yes	219 (95.2)	178 (92.2)	148 (88.1)	144 (87.8)
	Primary diagnosis[b]	Benign endometrium	219 (100.0)	176 (98.9)	147 (99.3)	143 (99.3)
		Hyperplasia	0	1 (0.6)	1 (0.7)	1 (0.7)
		Simple, nonatypical	0	1 (0.6)	0	0
		Complex, nonatypical	0	0	0	0
		Simple, atypical	0	0	0	0
		Complex, atypical	0	0	1 (0.7)	1
		Malignant neoplasm	0	1 (0.6)	0	0
		Endometrial adenocarcinoma[c]	0	1 (0.6)	0	0
		Other malignant neoplasm	0	0	0	0
	Polyps[b]	Absent	216 (98.6)	176 (98.9)	146 (98.6)	143 (99.3)
		Present: benign	3 (1.4)	2 (1.1)	1 (0.7)	1 (0.7)
		Present: hyperplasic	0	0	1 (0.7)	0
		Present: carcinomatous	0	0	0	0
	Of those with Benign endometrium	Nonphysiological changes observed by two or three pathologists[b]	17 (7.8)	29 (16.3)	24 (16.2)	13 (9.0)
UPA 10 mg (n = 221)	Endometrium Biopsy performed	Yes	220	194	163	160
	Specimen adequate[a]	Yes	203 (92.3)	182 (93.8)	145 (89.0)	142 (88.8)
	Primary Diagnosis[b]	Benign endometrium	203 (100.0)	180 (98.9)	145 (100.0)	142 (100.0)
		Hyperplasia	0	2 (1.1)	0	0
		Simple, nonatypical	0	1 (0.5)	0	0
		Complex, nonatypical	0	0	0	0
		Simple, atypical	0	1 (0.5)	0	0
		Complex, atypical	0	0	0	0
		Malignant neoplasm	0	0	0	0
		Endometrial adenocarcinoma	0	0	0	0
		Other malignant neoplasm	0	0	0	0
	Polyps[b]	Absent	199 (98.0)	180 (98.9)	142 (97.9)	142 (100)
		Present: benign	4 (2.0)	2 (1.1)	3 (2.1)	0
		Present: hyperplasic	0	0	0	0
		Present: carcinomatous	0	0	0	0
	Of those with benign endometrium	Nonphysiological changes observed by two or three pathologists[b]	17 (8.4)	35 (19.2)	15 (10.3)	9 (6.3)

Note: Numbers in parentheses are percents. In addition to cases of hyperplasia captured at nominated protocol visits, one consensus diagnosis of simple atypical hyperplasia was reported after the unscheduled histology review of material taken by curettage after the SAE of menorrhagia after treatment course 1. At early termination visit approximately 1 mo later, this subject had a consensus diagnosis of benign endometrium.
[a] Denominator of percentage is the number of subjects that have an endometrium biopsy performed.
[b] Denominator of percentage is the number of subjects with an adequate specimen.
[c] Preexisting condition.

Donnez. Ulipristal acetate in uterine fibroids. Fertil Steril 2015.

screening, the median levels of total cholesterol for the two groups were 4.93 and 5.03 mmol/L. The levels remained stable at each subsequent assessment, with medians ranging from 5.21 to 5.48. The median levels of low-density lipoprotein cholesterol for the two groups were 2.90 and 2.97 mmol/L at screening, and these remained stable at each subsequent assessment, with medians ranging from 2.99 to 3.23. Following the same pattern, at screening, the median levels of high-density lipoprotein cholesterol for the two groups were 1.61 and 1.55 mmol/L. The levels remained stable at each subsequent assessment across the treatment groups, with medians ranging from 1.64 to 1.71. Levels of triglycerides increased slightly during the study. At screening, the medians in the 5- and 10-mg groups were 0.87 and 0.91 mmol/L, respectively, increasing to median levels of 0.97 and 1.08 at the follow-up assessment (Supplemental Table 6). Further-

more, at screening, 27 (11.8%) and 30 (13.7%) subjects had high values (>ULN) for triglycerides in the 5- and 10-mg groups, respectively. Similarly at the follow-up assessment, 27 (16.0%) and 26 (15.6%) had high values in the two respective groups (Supplemental Table 7).

General Safety

The numbers (percentages) of subjects who reported AEs during treatment courses 1, 2, 3, and 4 were 102 (44.3%), 59 (27.4%), 32 (16.6%), and 43 (23.9%), respectively, for the 5-mg group and 98 (44.3%), 60 (29.3%), 38 (20.2%), and 33 (19.0%), respectively, for the 10-mg group (Supplemental Table 8). The numbers (percentages) of subjects who reported AEs considered as treatment related by the investigator during treatment courses 1, 2, 3, and 4 were 47 (20.4%), 28

FIGURE 1
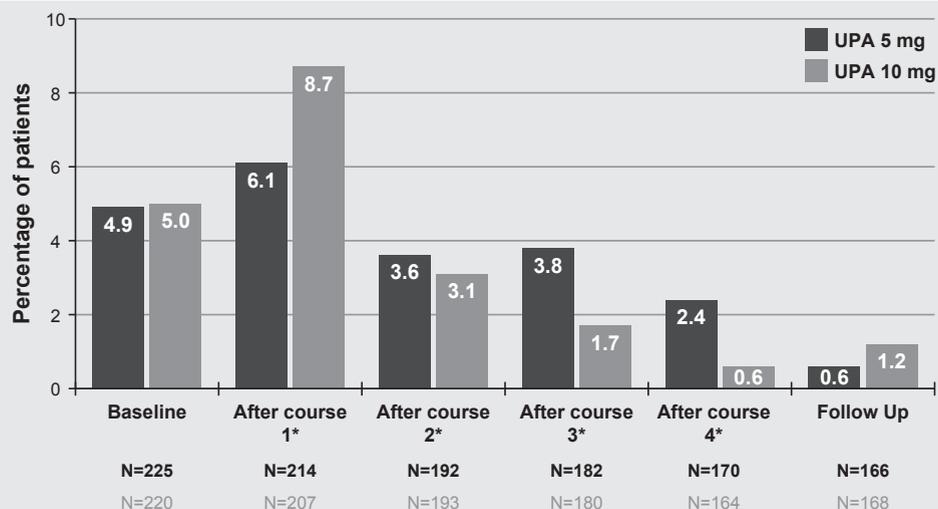
Percentage of patients with endometrial thickness >16 mm (safety population). *After treatment course + 1 bleed. N = number of patients in whom endometrial thickness was measured; UPA = ulipristal acetate.

Donnez. Ulipristal acetate in uterine fibroids. Fertil Steril 2015.

(13.0%), 9 (4.7%), and 11 (6.1%), respectively, for the 5-mg group and 43 (19.5%), 22 (10.7%), 12 (6.4%), and 14 (8.0%), respectively, for the 10-mg group. The vast majority of AEs (97.6%) were of mild or moderate severity in both groups.

Headaches and hot flushes were the most frequently reported AEs (≤11% of subjects in any treatment course), although the frequency of these events decreased with each successive treatment course (Supplemental Table 8). Breast pain/discomfort was observed in ≤3% of subjects, with a decrease in frequency for each successive treatment course (≤1% by treatment course 4). In total, 114 (25.3%) patients discontinued the study at any time and for any reason. Of those, 32 patients discontinued due to AEs, of which 21 were considered related to study drug. No difference between treatment groups was observed. Overall 34 serious adverse events (SAEs) were reported; 21 in the 5-mg group and 13 in the 10-mg group. Of these, 13 were classified by the investigator as related to study medication: nine in the 5 mg-group (five menorrhagia, one bipolar disorder, one spontaneous myoma expulsion, one abdominal pain, one back pain) and four in the 10-mg group (one partial expulsion, one spontaneous myoma expulsion, one myoma necrosis, one endometriosis).

No safety concerns were identified from physical examination, vital signs, ovarian ultrasound, and ECGs.

DISCUSSION

The PEARL IV study was designed to investigate the safety and efficacy of long-term, repeated intermittent treatment with four 12-week treatment courses of daily oral administration of either 5 or 10 mg of UPA in subjects with uterine fibroids. This is the first full clinical trial reporting the use of UPA 5 mg in a long-term repeated intermittent manner. Alternative treatment options previously available for the medical management of fibroids, such as GnRH agonists, could be used only for a limited period owing to the AE profile and rapid fibroid regrowth after treatment cessation (5). Among the latest possible therapeutic options (11), UPA has proved to be a suitable alternative for the medical management of fibroids.

Out of the 451 subjects with symptomatic uterine fibroids and confirmed menorrhagia recruited, 75% of subjects remained in the study on average a total of 20 months, demonstrating a good compliance with the protocol considering the duration of the study.

Investigation of the rate of amenorrhea during each treatment course showed that both UPA 5 and 10 mg led to amenorrhea in a high percentage of subjects (≥70%). Amenorrhea was reached on average within 1 week, and post-treatment menstrual bleeding was markedly reduced compared with pretreatment bleeding.

A high percentage of subjects were in amenorrhea for all treatment courses combined. The small observed difference between the treatment groups was within the predefined acceptable difference of 14% and was therefore not deemed to be clinically relevant. This was confirmed by the analysis of the group of subjects who had started all four courses, which found no statistically significant difference between the groups.

An additional secondary endpoint of importance in assessing the efficacy of UPA is the evaluation of bleeding control. No difference between the treatment groups was seen, with both groups showing ≥73% of subjects having bleeding control during each independent treatment course. These data confirm previously known data (4, 5, 7, 8) regarding the efficacy of UPA with regards to controlling bleeding symptoms in subjects with symptomatic uterine fibroids.

Furthermore, assessment of the blood loss during the first menstrual bleed after the treatment courses using the PBAC showed a marked progressive reduction from baseline with no difference between the two treatment groups.

Hb levels and associated hematology parameters increased over the first two treatment courses and were sustained until follow-up.

The total volume of the three largest myomas was shown to decrease after the first treatment course and was seen to further decrease after each subsequent treatment course. The reduction in volume was maintained thereafter until the end of study follow-up. A similar level of response was seen from both treatment groups with no statistically significant differences between them at any visit during the study. Furthermore, over 73% of all subjects had both fibroid volume reduction ≥ 25% at the end of four treatment courses in combination with being in amenorrhea (Supplemental Fig. 4).

For pain and QoL, an important improvement was recorded during treatment in these assessments, reaching scores reported for healthy individuals, in both treatment groups (3). The changes in these measurements were of a similar level between the two treatment groups. The results therefore show that the use of UPA results in an improvement in QoL and control of pain, in comparison to baseline, even during the off-treatment intervals.

After a transient increase in endometrial thickness in the first treatment course, fewer subjects had endometrial thickness >16 mm after each successive treatment course. No important differences with regards to endometrial thickness were observed between the 5- and 10-mg groups.

Over the entire observation period, six cases of hyperplasia were observed. All cases of hyperplasia observed after treatment returned to benign endometrium under continued treatment and/or during the follow-up period.

The occurrence of hyperplasia in a follow-up biopsy in a subject having been exposed to four courses of UPA and for whom all previous biopsies (including the one taken after the end of treatment course 4) had been diagnosed as benign endometrium by all pathologists illustrates that hyperplasia can occur spontaneously in this population.

Overall, the occurrence of nonphysiological changes of the endometrium was not increased with repetition of treatment courses and returned to pretreatment levels within 3 months of completion of treatment.

Levels of E_2 remained well above postmenopausal levels, suggesting that bone mineral density will not be adversely impacted by repeated intermittent use of UPA.

Mean levels of AST and ALT did not alter during the study; however, some sporadic increases were seen in individual subjects. In no subject were increases in transaminases associated with increases in bilirubin.

There were mild increases in mean cholesterol and triglyceride values during the study. At screening, 41.4% of all subjects had total cholesterol >ULN, and, as expected in such a long-term study recruiting women predominantly in their 40s, a number of subjects showed modest increases in cholesterol over the duration of the study (approximately 20 months). However, the median ratio of total cholesterol/high-density lipoprotein cholesterol remained virtually unchanged and below the level at which the risk of cardiovascular disease is considered to be increased.

More on-treatment AEs were reported during treatment course 1 than during subsequent treatment courses, and the most frequently reported on-treatment AEs were headache and hot flush. No other AE occurred at a frequency of >4% of subjects, and over 97% of all reported on-treatment AEs were rated as being of mild or moderate severity. Overall, there were no differences between the 5- and 10-mg dosing groups with respect to the type, frequency, and severity of AEs.

Conclusions

The current manuscript summarizes the full efficacy and safety results of the first randomized controlled trial using the approved dose of 5 mg UPA in a repeated, intermittent therapy setting (four courses) for the management of uterine fibroids.

The administration of four 12-week treatment courses of UPA at doses of 5 and 10 mg was well tolerated, with a high level of treatment compliance. No differences between the 5 and 10 mg dosing groups were recorded in terms of safety evaluations, which include a comprehensive evaluation of the endometrial characteristics and laboratory parameters observed with the long-term use of UPA.

In terms of efficacy, both doses provided efficient bleeding control leading to amenorrhea in the majority of subjects in each of the four treatment courses. This bleeding control was achieved very rapidly and was accompanied by a reduction in fibroid volume and a reduction of pain associated with a clinically significant improvement in QoL with both doses. Furthermore, even during off-treatment periods, the level of bleeding, pain, and QoL were still improved compared with baseline. Myoma reduction was largely maintained during the off-treatment periods, and these effects were sustained until the end of study follow-up, approximately 3 months after completion of the four treatment courses.

The results of this study therefore demonstrate the efficacy and further verify the safety profile associated with repeated intermittent treatment of symptomatic fibroids with UPA.

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ORIGINAL ARTICLE: GYNECOLOGY AND MENOPAUSE

SUPPLEMENTAL FIGURE 1

Schedule of treatments and visits.

Donnez. Ulipristal acetate in uterine fibroids. Fertil Steril 2015.

S1   1st visit to site, can be anytime. Subject trained to use ediary
S2   During menses
S3   10-18 days after menses

V2   1-4 days after start menses
V3   28 days after V2
V4   28 days after V3
V5   28 days after V4 (end of treatment 1)
V6   10-18 days after menses following treatment 1

V7   End of treatment 2 (equivalent V5)
V8   10-18 days after menses following treatment 2
V9   10-18 days after menses following treatment 3
V10   End of treatment 4
V11   10-18 days after menses following treatment 4
V12   Follow-up 3 months after last dose (mid-cycle)

Diary:
Bleeding: PBAC or simplified
Medication intake
Prompts for visits and meds
UFS QoL, pain VAS

UPA   UPA 5mg/10mg
  Menses
PBAC   Record PBAC
◆   Endometrium biopsy
◇   Endometrium biopsy, (if previous not adequate)
●   Site call to patient

SUPPLEMENTAL FIGURE 2

PBAC, one of the current standard methods used to objectively estimate menstrual blood loss and diagnose menorrhagia. The method that was developed and validated by Higham and Janssen defines excessive bleeding as a PBAC score >100.

Donnez. Ulipristal acetate in uterine fibroids. Fertil Steril 2015.

SUPPLEMENTAL FIGURE 3

```
                          ┌──────────────────┐
                          │     Screened     │
                          │      N=555       │
                          └──────────────────┘
                                                    ┌──────────────────┐
                                                    │ Screening failures│
                                                    │      N=104        │
                                                    └──────────────────┘

           ┌──────────────────┐   ┌──────────────────┐
           │  UPA 5mg group   │   │  UPA 10mg group  │
           │ Started treatment│   │ Started treatment│
           │     course 1     │   │     course 1     │
           │      N=228       │   │      N=223       │
           └──────────────────┘   └──────────────────┘
```

Withdrawn N=15
Subject request N=6
Adverse event N=6
Other reason N=2
Lack of efficacy N=1

Withdrawn N=16
Adverse event N=8
Subject request N=2
Other reason N=2
Not eligible N=1
Lack of efficacy N=1
Protocol deviation N=1
Surgery N=1

UPA 5mg group Started treatment course 2 N=213
UPA 10mg group Started treatment course 2 N=207

Withdrawn N=22
Subject request N=11
Other reason N=6
Adverse event N=4
Lack of efficacy N=1

Withdrawn N=17
Subject request N=8
Adverse event N=4
Other reason N=4
Surgery N=1

UPA 5mg group Started treatment course 3 N=191
UPA 10mg group Started treatment course 3 N=190

Withdrawn N=13
Other reason N=5
Subject request N=4
Adverse event N=4

Withdrawn N=14
Subject request N=9
Lack of efficacy N=2
Other reason N=1
Adverse event N=1
Pregnancy N=1

UPA 5mg group Started treatment course 4 N=178
UPA 10mg group Started treatment course 4 N=176

Withdrawn N=11
Subject request N=6
Adverse event N=2
Other reason N=1
Pregnancy N=1
Lost follow-up N=1

Withdrawn N=6
Adverse event N=3
Subject request N=1
Pregnancy N=1
Surgery N=1

UPA 5mg group Follow Up N=167
UPA 10mg group Follow Up N=170

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 UPA 10 mg group received UPA 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 4

Subjects in Amenorrhoea

	Yes	No
Yes	73.5%	7.8%
No	13.9%	4.8%

Clinically significant reduction in fibroid volume (>25%)

Amenorrhea and/or fibroid volume reduction. Percentage of subjects with amenorrhea and/or a clinically significant reduction in fibroid volume (>25%).

Donnez. Ulipristal acetate in uterine fibroids. Fertil Steril 2015.