Long-term treatment of uterine fibroids with ulipristal acetate☆

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Objective: To investigate the efficacy and safety of ulipristal acetate (UPA) for long-term treatment of symptomatic uterine fibroids.
Design: Repeated intermittent open-label UPA courses, each followed by randomized double-blind norethisterone acetate (NETA) or placebo.
Setting: European clinical gynecology centers.
Patient(s): Two hundred and nine women with symptomatic fibroids including heavy menstrual bleeding.
Intervention(s): Patients received up to four 3-month courses of UPA 10 mg daily, immediately followed by 10-day double-blind treatment with NETA (10 mg daily) or placebo.
Main Outcome Measure(s): Amenorrhea, fibroid volume, endometrial histology.
Result(s): After the first UPA course, amenorrhea occurred in 79% of women, with median onset (from treatment start) of 4 days (interquartile range, 2–6 days). Median fibroid volume change was −45% (interquartile range, −66%; −25%). Amenorrhea rates were 89%, 88%, and 90% for the 131, 119, and 107 women who received treatment courses 2, 3, and 4, respectively. Median times to amenorrhea were 2, 3, and 3 days for treatment courses 2, 3, and 4, respectively. Median fibroid volume changes from baseline were −63%,

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−67%, and −72% after treatment courses 2, 3, and 4, respectively. All endometrial biopsies showed benign histology without hyperplasia; NETA did not affect fibroid volume or endometrial histology.
Conclusion(s): Repeated 3-month UPA courses effectively control bleeding and shrink fibroids in patients with symptomatic fibroids.
Clinical trial registration: ClinicalTrials.gov (www.clinicaltrials.gov) registration numbers NCT01156857 (PEARL III) and NCT01252069 (PEARL III extension). (Fertil Steril® 2014; 101:1565–73. ©2014 by American Society for Reproductive Medicine.)
Key Words: Long-term treatment, ulipristal acetate, uterine fibroid

Leiomyomas or fibroids are benign hormone-sensitive tumors of uterine smooth-muscle cells, frequently involving point mutations and/or complex chromosomal rearrangements (1). They occur in about 20%–40% of women of reproductive age (2). Heavy menstrual bleeding (HMB), pelvic pressure and pain, and reproductive dysfunction are common symptoms that impair women's health and quality of life (QoL) (3, 4). Surgical interventions, especially hysterectomy, still predominate the treatment strategy (5). Options for medical therapy are currently limited to preoperative reduction of symptoms related to uterine bleeding and fibroid size; GnRH agonists are licensed but only for short-term therapy owing to safety concerns (loss of bone mass) and adverse reactions (hot flashes) (6, 7). The levonorgestrel-releasing intrauterine device, while not approved for this indication, has been found to reduce menstrual blood loss in women with uterine fibroids, but its efficacy is reduced in patients with a distorted uterus (8). Since February 2012, ulipristal acetate (UPA) is also approved in Europe for preoperative fibroid treatment (9). For the many women wishing to avoid surgery, there remains a substantial need for effective long-term medical therapy.

UPA is a selective P receptor modulator (SPRM) that potently modulates P-receptor activity (10) with proapoptotic/antiproliferative effects on fibroid cells (11) and with pharmacokinetic properties supporting once daily dosing (12). Two short-term (3 months) randomized clinical trials showed that UPA effectively controls HMB and shrinks fibroids (13, 14). After treatment cessation, menstruation usually returns within 4–5 weeks, but fibroid volume reduction can be sustained for up to 6 months. In addition, treatment with UPA reduced fibroid-associated pain, improved QoL, and revealed no safety concerns (13, 14). Clinical trials have also shown that SPRM administration can lead to a pattern of benign, nonphysiological, nonproliferative, histological features of the endometrium termed P receptor modulator associated endometrial changes (PAEC) (15–17). These changes spontaneously reverse over a few weeks to months after cessation of the 3-month UPA treatment (13, 14, 18). Hence, intermittent courses of 3-month UPA treatment with off-treatment intervals are a potential option for the long-term medical management of fibroids (9).

In these two studies, the PGL4001 (UPA) Efficacy Assessment in Reduction of Symptoms due to Uterine Leiomyomata (PEARL) III trial and its extension, we evaluated the sustained effects of UPA on menstrual bleeding, fibroid volume, pain, QoL, and safety during one to four 3-month UPA treatment courses.

Owing to the long-term treatment, no suitable active comparator to UPA was available. However, since UPA exerts mainly antiprogestagenic effects on the endometrium, we randomized women to receive 10 days of treatment with the progestin norethisterone acetate (NETA) or placebo (administered immediately after each completed UPA treatment) to explore any effect on the reversibility of PAEC or timing and magnitude of the next menstruation off treatment. The off-treatment period between each UPA course included one menstrual bleed and the beginning of a second bleed.

MATERIALS AND METHODS

Study Design and Oversight

PEARL III and its extension were long-term, open-label, phase III trials of UPA, which were double-blinded and placebo-controlled toward the administration of progestin after the end of each UPA treatment course. PEARL III was conducted at 21 investigation centers in four countries from July 2010 through November 2011, with 18 centers also participating in the extension protocol until January 2013. The trial and extension were approved by the independent ethics committee of each participating site and were conducted in accordance with the International Conference on Harmonisation Good Clinical Practice guidelines.

Study Population

PEARL III enrolled premenopausal women with at least one fibroid ≥ 3 cm in diameter and none >10 cm, HMB, and uterine size <16 weeks of gestation who were eligible for fibroid surgery. Eligible women were aged 18–48 years, 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 women. The main exclusion criteria are listed in Supplemental Table 1, available at www.fertstert.org.

Randomization and Intervention

Women received a 3-month open-label course of UPA (10 mg) once daily immediately followed by double-blind oral NETA (10 mg) once daily or matching placebo for 10 days allocated randomly in a 1:1 ratio.

UPA was started during the first 4 days of menstruation. After the first UPA (and NETA/placebo) treatment course and the return of menstruation, women could either leave the study and attend a final follow-up visit 12 weeks later (PEARL III) or, if they wished to be assessed for a further 18 months, enroll in the PEARL III extension study to obtain up to three further courses of UPA (and NETA/placebo), each separated by an off-treatment period including a full menstrual cycle up to the start of the second menstruation. Follow-up visits in the extension study were conducted approximately 3 months after the final treatment course. The sequence of treatments is illustrated in Supplemental Figure 1.

Efficacy endpoints

We evaluated efficacy and safety endpoints after the first treatment course (PEARL III), after each of up to three more treatment courses (PEARL III extension), and approximately 3 months after completion of the final treatment course. The primary efficacy endpoint was the occurrence of amenorrhea at the end of each UPA course. In accordance with previously published data, amenorrhea was defined as no bleeding for a continuous period of at least 35 days (1 day of spotting was allowed within any 35-day interval) to accurately describe the degree of bleeding control during UPA treatment under the conditions of this study (13, 14). This differs from the general definition of amenorrhea, which is three menstrual cycle lengths of no bleeding. Bleeding was assessed using a semiquantitative bleeding scale. For an exploratory endpoint, the Pictorial Blood-Loss Assessment Chart (PBAC) (19) was used to assess the magnitude of menstrual bleeding over 8 days at baseline (start of the first treatment course) and for the first menstruation after the end of each treatment course. A score greater than 100 indicates HMB.

Secondary efficacy endpoints included the reduction of the three largest fibroids identified at screening on the basis of ultrasound performed at each center. Further secondary endpoints were pain, measured with the Short-Form McGill Pain questionnaire (20) and QoL, measured by the general EQ-5D questionnaire (21) and by the specific Uterine Fibroid Symptom and Health-Related Quality of Life (UFS-QoL) questionnaire (22). Additional details are presented in the Supplemental Material.

Assessment of Safety Endpoints

Safety endpoints included the number and proportion of women experiencing treatment-emergent adverse events (TEAEs), including clinically significant changes in vital signs, physical examination, gynecological and/or breast examination, electrocardiogram (ECG), ovarian ultrasound, changes from baseline in endometrial thickness, and clinically significant changes in endometrial biopsy. The frequency and severity of adverse events (spontaneously reported or elicited by the investigators with the use of nonleading questions) were recorded on standard forms at every visit. Serious adverse events were recorded up to the last visit approximately 3 months after treatment cessation. Other safety endpoints comprised changes from baseline in hematology, coagulation, biochemistry, lipids, ACTH, TSH, and PRL, as well as serum levels of E_2.

Endometrial Histology

Endometrial biopsy samples were obtained 10–18 days after menstruation start during screening, after treatment courses 1 and 4, and 3 months after the end of course 4 in women with PAEC observed after course 4. All samples were assessed in a blinded manner by three independent pathologists experienced in PAEC.

Statistical Analysis

This study included open-label UPA treatment phases and placebo-controlled double-blinded NETA phases where assessments were considered exploratory. We planned to enroll 200 women, with approximately 80% of participants expected to fulfill the efficacy endpoint of amenorrhea at the end of the first UPA treatment course and allowing for a dropout rate of 10% during the first course of treatment. The planned sample size would provide an estimate of this percentage, with the corresponding 95% confidence interval (CI) being less than $\pm$6%. We considered 90 evaluable participants per treatment group to be sufficient to enable a reliable exploration of any differences between NETA and placebo treatment. We conducted efficacy and safety analyses using all women who started treatment course 1 (PEARL III open-label set) and two (PEARL III extension full analysis set). Endpoints were summarized using descriptive statistics. A 95% CI for the percentage of amenorrheic women was produced using the Wilson score method. The time from the start of dosing to amenorrhea was summarized as a continuous variable and presented using the Kaplan Meier probability estimates. The Wilcoxon rank sum test was performed to compare the placebo versus NETA treatment groups for the time to return to menstruation.

RESULTS

Patients

The baseline characteristics of the 209 participants who entered the study, the 132 who entered the extension study, and the 107 who received four treatment courses were very similar; most women were in their late 30s or early 40s with moderate to severe bleeding (the overall median PBAC was $>$200), and self-reported pain or discomfort and/or anxiety or depression (Table 1). Adverse events (eight women) and lack of efficacy (four women) were infrequent causes of study discontinuation (Supplemental Figs. 2 and 3).

Efficacy

Menstrual bleeding. At the end of the first treatment course, 164 women (78.5%) were amenorrheic (95% CI, 72.4%–83.5%; Supplemental Table 2). The median time to amenorrhea from treatment start was 3.5 days (interquartile range [IQR], 2–6 days).

For the 132 women who entered the extension study to receive multiple treatment courses, 88.5%, 88.2%, and

TABLE 1

Baseline (pretreatment course 1) characteristics for participants entering PEARL III and extension studies.

Characteristic	PEARL III only: open-label set (baseline data for women who started course 1), n = 209	PEARL III and extension study: full analysis set (baseline data for women who started at least two courses), n = 132	PEARL III and extension study: (baseline data for women who started all four courses), n = 107
Age, mean ± SD	40.1 ± 6.0	40.5 ± 5.8	40.8 ± 5.5
Race, n (%)[a]			
White	179 (85.6)	121 (91.7)	99 (92.5)
Black	19 (9.1)	8 (6.1)	5 (4.7)
Other	11 (5.3)	3 (2.3)	3 (2.8)
Body mass index, kg/m^2, mean ± SD	25.4 ± 4.4	25.4 ± 4.7	25.1 ± 4.6
Median (IQR) PBAC (days 1–8) score[b]	216 (126, 401)	235 (142, 397)	234 (132, 368)
Median (IQR) total volume of three largest fibroids, cm^3	53.9 (24.0, 128.7) (n = 207)	56.2 (25.7, 128.8) (n = 132)	49.8 (26.9, 112.8) (n = 107)
Median (IQR) uterine volume, cm^3	199.6 (125.2, 291.3) (n = 209)	200.7 (121.5, 303.1) (n = 132)	178.6 (116.6, 278.7) (n = 107)
Hemoglobin, g/dL, mean ± SD	12.5 ± 1.8 (n = 199)	12.4 ± 1.8 (n = 127)	12.5 ± 1.7 (n = 105)
Short-Form McGill Pain questionnaire[c] assessment of pain, median (IQR)	8.0 (3.0, 17.0) (n = 207)	8.0 (4.0, 19.0) (n = 131)	8.0 (4.0, 19.0) (n = 106)
Visual analog scale (VAS),[d] median (IQR)	38.0 (17.0, 63.0) (n = 209)	36.0 (17.0, 63.5) (n = 132)	37.0 (16.0, 63.0) (n = 107)
UFS-QoL questionnaire[e]			
Symptom severity, mean ± SD	47.7 ± 17.7 (n = 207)	49.2 ± 17.7 (n = 131)	49.0 ± 16.6 (n = 107)
Health-related QoL total score, mean ± SD	57.1 ± 20.9 (n = 208)	54.9 ± 20.6 (n = 132)	55.3 ± 19.9 (n = 107)
EQ-5D questionnaire	n = 209	n = 132	n = 107
Mobility (women with problems), n (%)	34 (16.3)	19 (14.4)	15 (14.0)
Self-care (women with problems), n (%)	5 (2.4)	2 (1.5)	1 (0.9)
Usual activities (women with problems), n (%)	50 (23.9)	26 (19.7)	22 (20.6)
Pain/discomfort (women with moderate or extreme symptoms), n (%)	154 (73.7)	102 (77.3)	84 (78.5)
Anxiety/depression (women with moderate or extreme symptoms), n (%)	129 (62.0[f])	85 (64.9[g])	74 (69.2)
VAS (health state),[h] mean ± SD	67.5 ± 18.6	67.9 ± 18.5	68.2 ± 17.6

Note: n = Number of women with nonmissing observations.
[a] Race or ethnic group was reported by the investigator.
[b] PBAC, measured during days 1–8 at the start of the UPA treatment (course 1).
[c] Scores on the Short-Form McGill Pain questionnaire range from 0 to 45, with higher scores indicating more severe pain.
[d] Scores on VAS range from 0 to 100, with higher scores indicating more severe pain.
[e] On the UFS-QoL questionnaire, scores for symptom severity range from 0 to 100, with higher scores indicating increased severity. Total scores for health-related QoL range from 0 to 100, with higher scores indicating a better QoL.
[f] n = 208.
[g] n = 131.
[h] Scores on VAS range from 0 to 100, with higher scores indicating a better health state.

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89.7% were in amenorrhea at the end of courses 2, 3, and 4, respectively (Table 2). The median times to amenorrhea after the start of each course were 2, 3, and 3 days for courses 2, 3, and 4, respectively (Fig. 1A). The percentages of women with only spotting or no bleeding were 93.9%, 94.1%, and 93.5% at the end of courses 2, 3, and 4, respectively.

After the end of each treatment course, menstruation resumed. Menstrual bleeding (PBAC days 1–8) progressively reduced from medians of 228 and 257 at the start of the first course to 55 and 13 after the end of the fourth UPA course for women randomized to placebo or NETA, respectively ($P=.02$; Supplemental Table 3). Thus, 10-day progestin courses reduced the magnitude of menstrual bleeding during the off-treatment periods and also brought forward menstruation return (e.g., median of 15 days instead of 30 days for women receiving placebo after the end of the fourth UPA treatment course; $P<.001$).

Fibroid volume. The median change from baseline to end of the first UPA treatment course in the combined volume of the three largest fibroids was −45.1% (IQR, −66.1 to −24.9%; Supplemental Table 2). For women receiving multiple treatment courses, fibroids continued to shrink, reaching a median volume reduction of −72.1% after four treatment courses (Table 2, Fig. 1B). This volume reduction was mostly maintained (median −58.8%) at follow-up 3 months after the end of the fourth treatment course. Of women completing four treatment courses, 82.3% and 69.8%, respectively, had ≥25% and ≥50% reductions in volume of the three largest fibroids.

Pain and QoL. During the first treatment course, improvements in pain were apparent from the fifth week onward and were generally maintained for all UPA treatment periods (Table 2, Supplemental Table 2). UFS-QoL scores indicated substantially reduced QoL at baseline, but mean scores were within the range of healthy participants at the end of each treatment course and the improvement was largely maintained at 3-month follow-up after the final treatment course. The EQ-5D questionnaire showed that most women had

TABLE 2

Efficacy results for participants entering PEARL III extension study (PEARL III extension full analysis set).[a]

	Course 1	Course 2	Course 3	Course 4	3 Month follow-up
Amenorrhea, n/N (%)	105/132 (79.5)	116/131 (88.5)	105/119 (88.2)	96/107 (89.7)	–
95% CI, %	71.9, 85.5	82.0, 92.9	81.2, 92.9	82.5, 94.2	–
Spotting or no bleeding, n/N (%)	117/132 (88.6)	123/131 (93.9)	112/119 (94.1)	100/107 (93.5)	–
% Change in total volume of three largest fibroids[b] from baseline, median (IQR)	−49.9 (−69.0, −27.2) (n = 130)	−63.2 (−76.4, −38.3) (n = 119)	−67.0 (−79.9, −33.5) (n = 106)	−72.1 (−86.6, −35.7) (n = 96)	−58.8 (79.2, −21.0) (n = 97)
Total reduction ≥25%, n (%)	101 (77.7)	95 (79.8)	83 (78.3)	79 (82.3)	70 (72.2)
Total reduction ≥50%, n (%)	65 (50.0)	77 (64.7)	66 (62.3)	67 (69.8)	56 (57.7)
% Change in uterine volume from baseline, median (IQR)	−29.8 (−45.2, −10.5) (n = 132)	−32.3 (−47.1, 0.7) (n = 121)	−29.9 (−47.5, −1.8) (n = 107)	−40.2 (−55.6, −15.3) (n = 96)	−22.3 (−46.2, 5.5) (n = 99)
Reduction ≥25%, n (%)	73 (55.3)	73 (60.3)	61 (57.0)	64 (66.7)	45 (45.5)
Assessment of pain					
Short-Form McGill Pain questionnaire	n = 131	n = 119	n = 108	n = 96	n = 96
Actual, median (IQR)	1.0 (0.0, 3.0)	1.0 (0.0, 4.0)	1.0 (0.0, 6.0)	1.0 (0.0, 2.0)	2.0 (0.0, 7.0)
Change from baseline, median (IQR)	−7.0 (−15.0, −2.0)	−6.0 (−14.0, −2.0)	−5.0 (−13.5, 0.0)	−6.0 (−16.0, −2.0)	−4.0 (−11.0, 0.0)
VAS[c]	n = 132	n = 120	n = 109	n = 96	n = 98
Actual, median (IQR)	1.0 (0.0, 11.0)	3.0 (0.0, 13.5)	2.0 (0.0, 13.0)	1.5 (0.0, 8.5)	7.0 (1.0, 29.0)
Change from Baseline, median (IQR)	−23.5 (−58.0, −6.5)	−27.5 (−54.0, −7.0)	−25.0, (−49.0, −6.0)	−30.5 (−54.0, −10.0)	−17.0 (−42.0, −2.0)
UFS-QoL questionnaire[d]					
Symptom severity	n = 129	n = 117	n = 104	n = 91	n = 98
Actual, mean ± SD	13.4 ± 15.3	18.4 ± 16.8	20.5 ± 19.5	17.9 ± 17.1	27.1 ± 21.1
Change from baseline, mean ± SD	−35.8 ± 21.2	−30.5 ± 21.9	−27.7 ± 23.3	−30.0 ± 20.3	−21.2 ± 22.1
Health-related QoL total score	n = 131	n = 117	n = 108	n = 96	n = 99
Actual, mean ± SD	87.8 ± 14.8	85.2 ± 16.4	85.2 ± 18.1	87.5 ± 16.2	79.2 ± 22.9
Change from baseline, mean ± SD	32.8 ± 21.9	29.6 ± 22.4	29.4 ± 23.4	31.4 ± 21.6	22.7 ± 22.5
EQ-5D questionnaire	n = 132	n = 121	n = 109	n = 96	n = 99
Mobility (women with problems), n (%)	6 (4.5)	3 (2.5)	5 (4.6)	4 (4.2)	3 (3.0)
Self-care (women with problems), n (%)	0	0	1 (0.9)	0	0
Usual activities (women with problems), n (%)	6 (4.5)	3 (2.5)	4 (3.7)	3 (3.1)	7 (7.1)
Pain/discomfort (women with moderate or extreme symptoms), n (%)	33 (25.2[e])	31 (25.6)	26 (24.1[f])	23 (24.0)	37 (37.4)
Anxiety/depression (women with moderate or extreme symptoms), n (%)	49 (37.1)	27 (22.3)	33 (30.3)	29 (30.2)	37 (37.4)
VAS (health state)[g]	n = 132	n = 120	n = 109	n = 95	n = 99
Actual, mean ± SD	78.1 ± 18.0	81.2 ± 14.9	83.4 ± 13.5	84.4 ± 15.5	84.1 ± 14.9
Change from baseline, mean ± SD	10.2 ± 23.8	13.3 ± 21.3	15.6 ± 20.2	15.2 ± 20.3	14.8 ± 18.9

Note: n = Number of women with nonmissing observations.

[a] Amenorrhea (and spotting or no bleeding) assessed while under UPA treatment. For remaining results, courses 1 and 4 data were collected at the end of UPA treatment; courses 2 and 3 data were collected after the first menstrual bleed after UPA treatment and subsequent NETA/placebo treatment.

[b] The same three fibroids identified at screening were followed throughout the study.

[c] Scores on VAS range from 0 to 100, with higher scores indicating more severe pain.

[d] On the UFS-QoL questionnaire, scores for symptom severity range from 0 to 100, with higher scores indicating increased severity. Total scores for health-related QoL range from 0 to 100, with higher scores indicating a better QoL.

[e] n = 131.

[f] n = 108.

[g] Scores on VAS range from 0 to 100, with higher scores indicating a better health state.

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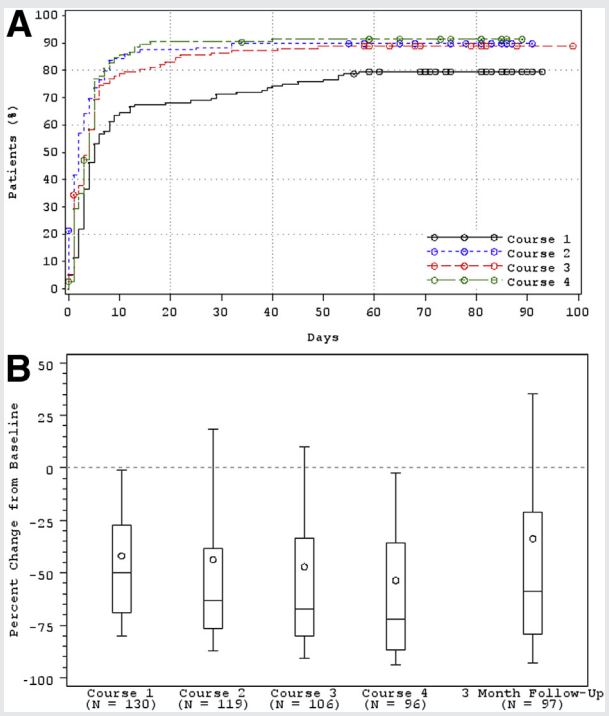
FIGURE 1



(A) Time to no bleeding (persistent amenorrhea; PEARL III extension full analysis set). Time to amenorrhea was defined as the first day for which there was subsequently no bleeding for longer than 35 days to the end of UPA treatment within each treatment course, assessed using the patient diary data from the date of the first dose of UPA (day 0, which was to be within the first 4 days of the start of menstruation for treatment courses 1 and 2 and on the first day of menstruation for treatment courses 3 and 4). One day of spotting in any 35-day interval was accepted. Circles denote censored observation (i.e., a participant had a subsequent interval of 35 days or less up to the end of UPA treatment for which no more than 1 day of spotting was observed). (B) Percent change from baseline in total volume of the three largest fibroids (PEARL III extension full analysis set). N = number of women with nonmissing observations. The same three fibroids identified at screening were followed throughout the study. Box extends to 25th and 75th percentiles (IQR) and shows median value. Mean values are also plotted. Whiskers extend to 10th and 90th percentiles. Courses 1 and 4 data were collected at the end of UPA treatment; courses 2 and 3 data were collected after the first menstrual bleed after UPA treatment and subsequent NETA/placebo treatment.

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discomfort or pain and/or anxiety and depression at baseline, but few women reported these conditions at the end of each UPA treatment course and at 3-month follow-up (Tables 1 and 2).

Surgery and enrollment in extension study. A total of 132/209 patients consented and proceeded to the extension phase of the study. Among them were 64/91 women for whom surgery was planned at baseline (Supplemental Fig. 2). There were no significant differences in baseline disease severity between women who entered the extension study and those who did not.

After one course of treatment, UPA exerted similar control over bleeding and pain for patients entering the extension study (compared with those who did not). Women entering the extension study had a somewhat greater reduction in median fibroid volume (−49.9% vs. −38.5%) and greater improvement in UFS-QoL (least square mean change, 31.2 vs. 25.3) after one course of UPA compared with those who did not enter the second study (Supplemental Table 4).

Safety

General safety. There were no serious adverse events (SAEs) reported during the first course of UPA treatment, but two women had three post-treatment SAEs (two episodes of uterine bleeding and one breast cancer) that were considered not related to study medication. Seven women who entered the extension study (and received multiple courses of treatment) reported SAEs (five cases of uterine bleeding, one thyroid cyst, and one chlamydia infection; Table 3).

During the first course of UPA treatment, TEAEs occurred in 120 women (57.4%; Supplemental Table 5), but only eight women (3.8%) had severe AEs. Only one TEAE (headache) led to treatment withdrawal. TEAEs occurring in >5% of women were headache (16.3%), nasopharyngitis (6.7%), and abdominal pain (5.3%). In women receiving multiple treatment courses, headaches, nasopharyngitis, abdominal pain, and hot flashes were the most frequent TEAEs, but the incidence did not increase over time and only five women discontinued UPA because of TEAEs (Table 3).

There were no safety signals arising from physical examination, vital signs, liver function, and other laboratory safety tests, hormone levels, ovarian ultrasound, and ECGs (see Supplemental Table 6).

Endometrial safety. Transient increases in endometrial thickness occurred in less than 10% of women after each UPA course (Supplemental Table 6). No cases of endometrial hyperplasia or adenocarcinoma were reported at any time point for any woman.

Nonphysiological features were reported by at least two pathologists for 18/171 (11%), 45/176 (26%), and 22/87 (25%) women biopsied at screening and at approximately 6 weeks after courses 1 and 4, respectively (Supplemental Table 7). Fifteen women with PAEC diagnosed after the fourth UPA course were rebiopsied 3 months later; only three had some nonphysiological features. Ten days of NETA did not have a significant impact on the incidence of nonphysiological changes induced by UPA.

DISCUSSION

In these sequential studies of women with fibroids and excessive menstrual bleeding, we administered intermittent courses of UPA. Women had the option of surgery after one course, but for many women the goal is to avoid surgery and most decided to enroll into the extension study where they could receive up to three additional courses even if surgery was planned at baseline. Intermittent UPA (administered over an 18-month period) induced high rates of amenorrhea (nearly 90% during repeat treatment courses), confirming its ability to control for the long term the most troublesome symptom

TABLE 3

Adverse events (PEARL III extension safety set).[a]

Adverse event, no. of women (%)	Overall (n = 132)	Course 1 (n = 132)	Course 2 (n = 131)	Course 3 (n = 119)	Course 4 (n = 107)
SAEs					
At least one SAE	7 (5.3)	0	2 (1.5)	2 (1.7)	3 (2.8)
Any SAE during UPA treatment	6 (4.5)	0	2 (1.5)	2 (1.7)	2 (1.9)
HMB	2 (1.5)	0	1 (0.8)	0	1 (0.9)
Uterine hemorrhage	2 (1.5)	0	1 (0.8)	0	1 (0.9)
Metrorrhagia	1 (0.8)	0	0	1 (0.8)	0
Thyroid cyst	1 (0.8)	0	0	1 (0.8)	0
Any SAE during NETA/placebo treatment	0	0	0	0	0
Any SAE off treatment	1 (0.8)	0	0	0	1 (0.9)
Chlamydial infection	1 (0.8)	0	0	0	1 (0.9)[b]
Adverse events[c]					
Leading to study withdrawal[d]	5 (3.8)	0	1 (0.8)	2 (1.7)	2 (1.9)
At least one event	91 (68.9)	73 (55.3)	27 (20.6)	35 (29.4)	37 (34.6)
Headache	26 (19.7)	19 (14.4)	4 (3.1)	6 (5.0)	7 (6.5)
Nasopharyngitis	18 (13.6)	10 (7.6)	3 (2.3)	1 (0.8)	6 (5.6)
Abdominal pain (including upper/lower)	12 (9.1)	7 (5.3)	3 (2.3)	1 (0.8)	2 (1.9)
Hot flashes	12 (9.1)	7 (5.3)	1 (0.8)	5 (4.2)	1 (0.9)
Back pain	8 (6.1)	2 (1.5)	0	4 (3.4)	2 (1.9)
Fatigue	8 (6.1)	4 (3.0)	0	3 (2.5)	3 (2.8)
Nausea	8 (6.1)	4 (3.0)	2 (1.5)	1 (0.8)	1 (0.9)
Vertigo	7 (5.3)	6 (4.5)	0	1 (0.8)	1 (0.9)
Hair loss	6 (4.5)	5 (3.8)	1 (0.8)	2 (1.7)	0
Breast discomfort/breast pain/breast tenderness	6 (4.5)	4 (3.0)	0	1 (0.8)	1 (0.9)

[a] All SAEs and all adverse events that occurred during UPA treatment in at least 4% of women overall are included.
[b] SAE was diagnosed 3 months after treatment course 4.
[c] Adverse events with onset on or after the first dose of UPA and before the first dose of NETA/placebo within each treatment course or up to and including 7 days after the last dose of UPA if NETA/placebo was never started.
[d] In addition, another adverse event that occurred when a woman was not receiving UPA led to study withdrawal.

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of fibroids for most women. The previously reported efficacy of UPA in shrinking fibroids was also confirmed, and there was further fibroid shrinkage with successive treatment courses with no evidence of rapid rebound growth. However, even in women with little or no fibroid shrinkage, UPA still induced high rates of bleeding control (Supplemental Table 8). Women also reported substantial improvements in pain, anxiety and depression, and QoL during treatment. The UFS-QoL scores at baseline were slightly less severe than reported in some previous studies of patients undergoing invasive treatments; however, at the end of each UPA course, symptom severity and QoL scores were similar to those reported at follow-up for patients who underwent hysterectomy, myomectomy, uterine artery embolization, high-intensity focused ultrasound, or experimental treatment with mifepristone (23–26).

It might have been expected that fibroid-related symptoms would partially return during off-treatment periods, but the magnitude of menstrual bleeding (after the end of each treatment course) progressively diminished. Moreover, at 3 months after the last treatment course, the reduction in fibroid volume and the improvements in pain and QoL were largely maintained. These findings, together with previous observations (11) that UPA can induce apoptosis and decrease proliferation in fibroid cells, suggest that long-term intermittent SPRM therapy could result in disease regression.

Most adverse events were mild or moderate and did not increase in frequency with successive treatment courses. The most frequently reported SAE was excessive uterine bleeding, but considering that women were monitored for over 18 months, the incidence of this finding is not greater than that reported in previous studies of UPA, placebo, and comparator agents in women with fibroid-related HMB (13, 14).

Some of the nonphysiological features of PAEC can be observed in women of reproductive age in the absence of pharmacotherapy (>10% incidence at screening in this study) (18). Donnez et al. previously reported that 3-month courses of UPA induce PAEC in approximately 60% of women and that this is fully reversible 6 months after the end of the treatment (13, 14). In this study, the endometrium was biopsied approximately 6 weeks after the end of the first and fourth courses of UPA treatment, and PAEC was diagnosed in approximately 25% of women at both time points. Similar incidences of PAEC after one and four courses of treatment indicate that treatment duration and cumulative dose do not affect occurrence of PAEC during prolonged, intermittent UPA administration. In the small subgroup of women with PAEC diagnosed after the fourth UPA course, the PAEC diagnosis rate at 3 months follow-up was the same as at screening, confirming that PAEC is rapidly reversible in most women after successive on/off administration. No cases of endometrial hyperplasia or adenocarcinoma were observed.

A 10-day course of progestin, administered immediately after each UPA treatment course, did not affect PAEC but was associated with a significantly reduced and

an earlier occurrence of menstrual bleeding during the off-treatment periods. However, these findings are probably insufficient to suggest that progestins should be routinely used in conjunction with UPA treatment unless there is a need to control the timing or amount of menstrual bleeding, for example, before a planned invasive procedure.

Currently, there are no approved long-term medical treatment options for the management of women with symptomatic fibroids. Some clinicians have attempted to use GnRH agonists with hormonal add-back therapy, but women still have menopausal symptoms, rates of bone mass loss may not be entirely mitigated, and fibroids rapidly enlarge after treatment is stopped (7). There are abundant P receptors in fibroids, and oral progestins (alone) have been used but without evidence that they shrink fibroids and with risk of breakthrough bleeding (27, 28). Intrauterine levonorgestrel does not consistently reduce fibroid volume, and its efficacy in women with submucous fibroids or a distorted uterus is controversial (8). Thus our results suggest that intermittent UPA could become the first long-term medical management option for many women with symptomatic fibroids.

There are some limitations to our study. We could not use an active or placebo control for long-term UPA treatment. However, it was previously demonstrated that a 3-month course of UPA was superior to placebo and noninferior to a GnRH agonist for control of HMB (13, 14). The dose (10 mg) and duration of each UPA course (3 months) were based on previous experience, but it is unknown whether longer periods of continuous treatment could also be safe and effective. We also recruited relatively few black participants, but previous studies reported efficacy in these women (13, 14, 29, 30). We also restricted fibroid size to a maximum diameter of 10 cm, but we note that the median diameter of the largest fibroid in a series of patients undergoing hysterectomy, myomectomy, or uterine artery embolization was 6 cm (24). Approximately one-third of women (some of whom had surgery) did not enroll in the extension study, and so we cannot be certain how this subset of patients would have responded to repeated UPA treatment courses. Women who received only one UPA treatment course achieved similar levels of bleeding control to those participating in the extension study, although improvements in QoL and fibroid volume reduction were slightly less substantial.

In conclusion, repeated 3-month courses of oral UPA 10 mg once daily effectively control bleeding and pain, reduce fibroid volume, and restore QoL over the long term in many women with symptomatic fibroids, providing an effective and well-tolerated long-term medical treatment for fibroids.

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SUPPLEMENTAL MATERIALS

Donnez. Long-term treatment of uterine fibroids. Fertil Steril 2014.

This appendix has been provided by the authors to give readers additional information about their work. The full protocols of the clinical trials are available on request to Dr Elke Bestel, M.D., Chief Medical Officer, PregLem S.A., Switzerland (E-mail: elke.bestel@preglem.com).

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MATERIALS AND METHODS

Study Population

Dates of the study period. PEARL III only: July 13, 2010, to November 10, 2011.

PEARL III + PEARL III extension: July 13, 2010 to January 24, 2013.

The study ended after the last follow-up of the last patient as foreseen in the protocol.

Principal exclusion criteria. The principal exclusion criteria for the study are listed in Supplemental Table 1. The body mass index was calculated using the body weight in kilograms divided by the height in meters squared.

Randomization and masking. All women received open-label treatment with UPA. UPA treatment courses were equal to 90 days of UPA treatment. Women consented to participate to one treatment course (PEARL III study). Approximately 8 weeks into treatment course 1, women were randomized to receive double-blind treatment with either NETA or matching placebo after a predefined order and according to a predefined randomization list that had been established by the designated unblinded statistician at MDSL International with the corresponding treatment supplied at the end of the first course of UPA. The NETA or placebo were packaged in blisters of identical appearance. The treatment packs were assigned within each site by the investigator to the subjects in sequential order starting from the lowest number to the highest number.

After completion of the first treatment period, patients were proposed to participate in an extension study (PEARL III extension) with three further UPA treatment courses. The women received the same double-blind treatment of NETA or placebo throughout all treatment courses. Double-blinding was maintained for women and investigators throughout the entire study. At the end of the PEARL III study, the blind was broken for selected sponsor members to fulfill regulatory reporting requirements.

Efficacy Endpoints

Assessment of menstrual bleeding. The proportion of women in amenorrhea at the end of each UPA treatment course and the time to onset of amenorrhea for each treatment course were evaluated. Amenorrhea was defined as no bleeding for a continuous period of at least 35 days. Within any 35-day interval, 1 day of spotting was accepted. To assess this endpoint, we used a simplified semiquantitative bleeding scale, which included four categories: "no bleeding," "spotting," "bleeding," or "heavy bleeding." During the first treatment course the diary was completed daily with four categories available, whereas during subsequent treatment courses, women only reported spotting, bleeding, or heavy bleeding on days when these occurred (Supplemental Fig. 4A and B show sample charts). The proportion of women with "spotting"/"no bleeding" (that is, no "bleeding" or "heavy bleeding") and the time to onset of "spotting"/"no bleeding" for each treatment course was also evaluated.

The PBAC (1–4), an instrument that estimates menstrual blood loss in a semiquantitative measure, was used to evaluate the magnitude of menstrual bleeding at the start of the first treatment cycle and during the off-treatment period after each treatment course. PBAC has been widely used for evaluating drugs or devices interfering with menstrual bleeding such as desmopressin (5), tranexamic acid (6), ormeloxifene (7), levonorgestrel intrauterine device (8), and devices for endometrial ablation (9). The possible score ranges from 0 to more than 500 (with no defined upper limit), with higher scores indicating a greater severity of bleeding. Scores greater than 100 indicate HMB (1). Standardized sanitary materials were provided, and women recorded the number of tampons or pads used and the extent of soiling with blood. A sample chart is presented in Supplemental Figure 4C. The PBAC was completed by women during the first 8 days of their menstrual cycle at the start of treatment course 1 to have an objective assessment of the bleeding intensity and during the first 8 days of the first menstrual cycle after each NETA/placebo treatment.

Secondary efficacy endpoints. The volume of the three largest fibroids was assessed using transvaginal ultrasound (TVUS). The same three fibroids identified during screening were followed throughout the study. TVUS also included an assessment of the ovaries, uterine volume, endometrial thickness, and deformation of the uterine cavity and was performed at baseline, at the end of UPA treatment for course 1, and for subjects continuing in the extension study: 2 weeks after the start of first menses after treatment courses 2 and 3, at the end of UPA treatment course 4, and approximately 3 months after the end of the final treatment course.

Pain was measured with the Short-Form McGill Pain questionnaire (SF-MPQ) (10). The SF-MPQ part A consists of 15 descriptors that are ranked on an intensity scale of 0 = none to 3 = severe. Descriptors 1–11 represent the sensory (S) dimension of the pain experience, and 12–15 represent the affective (A) dimension. The total score for S is obtained by adding the ranks from descriptors 1–11. The total score for A is obtained by adding the ranks from descriptors

12–15. The overall total score is then obtained by adding the scores for S and A. If either the score for A or S is missing, then the overall total score will also be missing. Scores for SF-MPQ part A range from 0 (no pain) to 45 (severe pain for every S and A descriptor). SF-MPQ part B consists of a visual analog scale (VAS), with the resulting score between 0 mm and 100 mm; scores range from 0 (no pain) to 100 (worst possible pain). The SF-MPQ was assessed at baseline, at the end of weeks 4 and 8, and at the end of UPA treatment for the first treatment course, as well as for subjects continuing in the extension study 2 weeks after the start of first menses after treatment courses 2 and 3, at the end of UPA treatment for course 4, and approximately 3 months after the end of the final treatment course.

QoL was assessed using the Uterine Fibroid Symptom and Health-Related Quality of Life (UFS-QoL) questionnaire (11). The UFS-QoL is a validated, disease-specific questionnaire that consists of two parts; [1] a symptom severity score that includes bleeding, abdominal pressure, urination frequency, and fatigue (range, 0–100) with high symptom severity scores indicating increased symptom severity; and [2] a health-related quality of life (HRQL) total score. The HRQL total score (range, 0–100) is composed of six domains: Concern, Activities, Energy/Mood, Control, Self-Conscious, and Sexual Function. High HRQL scores indicate better QoL. Furthermore, another measure of QoL was assessed using the EQ-5D questionnaire, a standardized instrument for use as a measure of health outcome that consists of five dimensions of health status: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, all with a three-level scale. It also includes a VAS ranging from zero to 100, with lower scores indicating a worse health state. QoL assessments were recorded at the same time points as the volume of fibroids.

Safety Endpoints

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. All pathologists have participated in previous UPA studies (12). Assessments were made according to standard diagnostic criteria and terminology for nonphysiological endometrial changes (p-receptor modulator–associated endometrial changes or PAEC), as described elsewhere by Mutter and colleagues (13). A consensus diagnosis of PAEC was made if two or more pathologists observed nonphysiological changes in an endometrial biopsy specimen. The timing of endometrial biopsies is presented in Supplemental Figure 1. Additional samples could be taken if endometrial thickness was >18 mm or if judged necessary by the investigator.

Clinical laboratory testing (hematology, biochemistry, and coagulation) was performed in a central laboratory (ICON Central Laboratories Ltd.) using validated assays. Laboratory investigations and vital signs were assessed at all visits. Serum E_2, ACTH TSH and PRL levels were measured at screening, at the end of UPA treatment for courses 1 and 4, 2 weeks after the start of first menses after treatment course 2, and approximately 3 months after the end of the final treatment course. The FSH level was measured at screening.

Statistical Analyses

Data management and statistical analysis were conducted using SAS 9.2 and governed by a comprehensive quality assurance system following International Conference on Harmonisation (14) and other applicable regulatory guidelines.

RESULTS

Supplemental Table 2 presents efficacy results for the first treatment course in the PEARL III open-label set.

The individual decisions on whether to have surgery or enter the extension study and to continue successive treatment courses may depend on many factors including advice of the investigator or surgeon, the response to treatment, and the patient's own preference for continued treatment and to adhere to all the study visits and procedures. The women's baseline characteristics and the overall response to course 1 (amenorrhea, fibroid volume reduction, pain, and QoL) were similar for women who continued into the extension study compared with all women who started PEARL III. Only four women discontinued PEARL III extension owing to lack of efficacy, and an analysis (not shown) of women who completed all four courses of treatment indicates that there were improvements in amenorrhea rates and fibroid volume reduction with successive treatment courses.

Supplemental Table 3 presents a summary of volume and timing of first menstruations during off-treatment periods for the PEARL III double-blind set (all women who received NETA or placebo at the end of UPA treatment for treatment course 1) and the PEARL III extension full analysis set), split by the NETA and placebo treatment groups and overall.

Supplemental Table 8 presents the proportion of women in amenorrhea at the end of each treatment course according to whether the total volume of the three largest fibroids was reduced by $\geq$ 25%.

Supplemental Table 4 presents a summary of relevant efficacy results after the first UPA treatment course comparing women not entering the PEARL III extension study with those who decided to participate in an extension study with up to three additional treatment courses. Both subgroups had similar disease severity at baseline and efficacy response to one course of UPA.

Supplemental Table 5 presents a summary of adverse events in the PEARL III safety set (for the first treatment course).

Five women discontinued the extension study owing to adverse events. These were women with heavy uterine bleeding (n = 1) after the end of course 2, metrorrhagia (n = 1) during course 3, vertigo/dyspepsia/abdominal cramps and constipation during course 3, high blood pressure (n = 1) during course 4, and heavy uterine bleeding (n = 1) during course 4. Another woman discontinued the study due to leg pain that started 2 months after the end of course 2.

Supplemental Table 7 shows a summary of pathologist consensus of nonphysiological histological features in the endometrium.

Supplemental Tables 6 and 9 present summaries of other safety assessments in the PEARL III safety set and the PEARL III extension safety set.

Supplemental Figure 5 presents the time to spotting/no bleeding for each treatment course for the PEARL III extension full analysis set.

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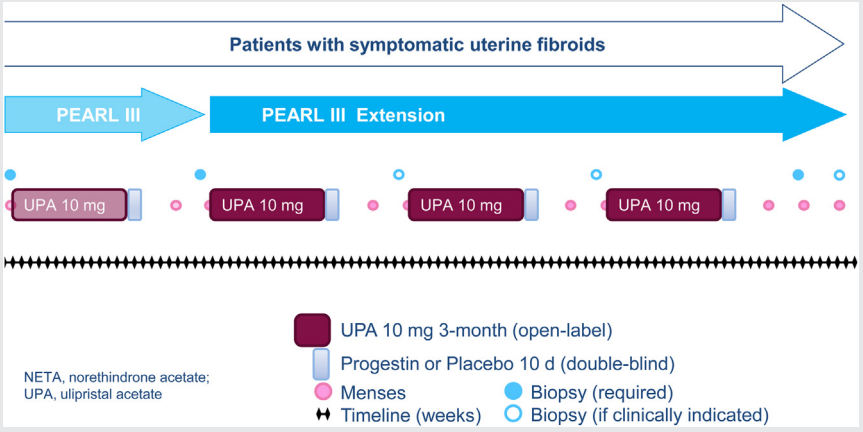
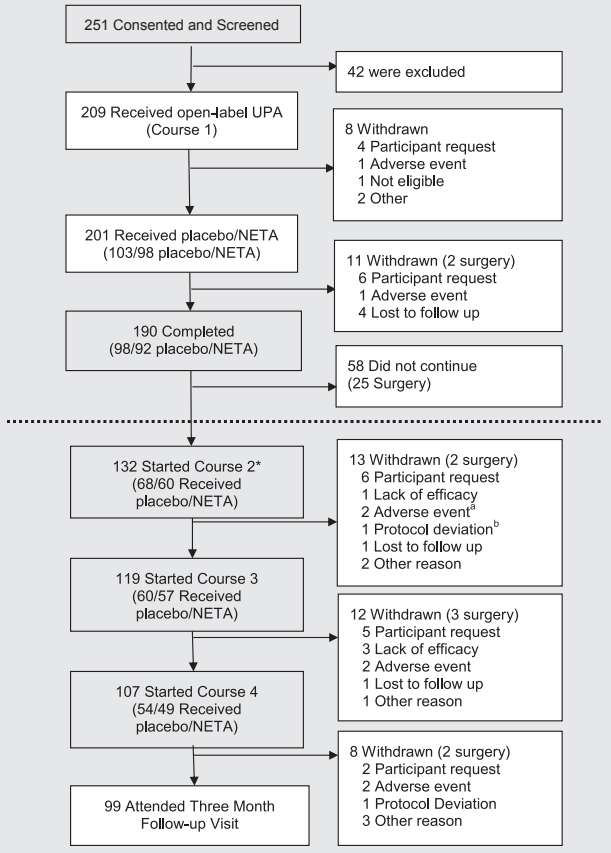
SUPPLEMENTAL FIGURE 1



Pictorial flow diagram of treatments and biopsies for PEARL III and extension study.

Donnez. Long-term treatment of uterine fibroids. Fertil Steril 2014.

SUPPLEMENTAL FIGURE 2



Patient disposition for participants entering PEARL III and PEARL III extension. [a]Includes one woman who was withdrawn owing to an adverse event occurring in an off-treatment period. [b]One woman was treated correctly for treatment course 1 but received only placebo medication (no UPA) in error for treatment course 2.

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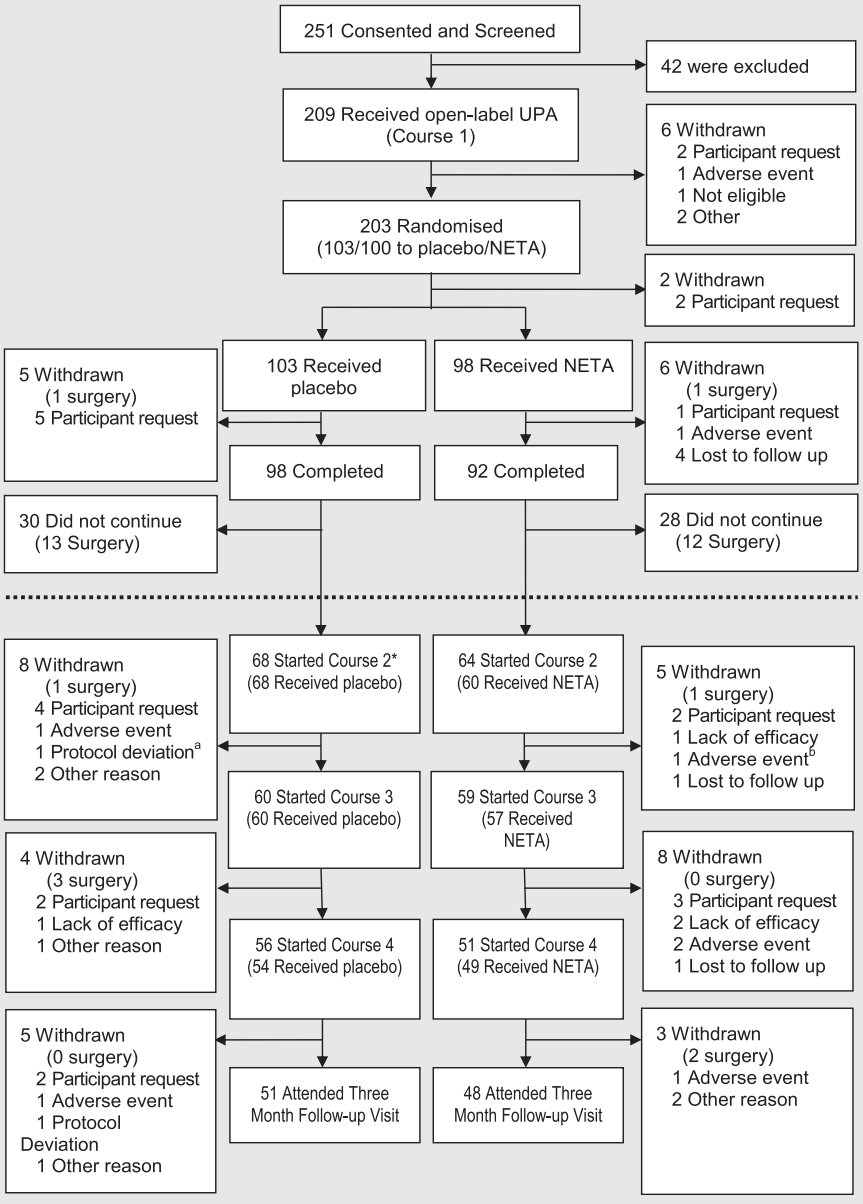
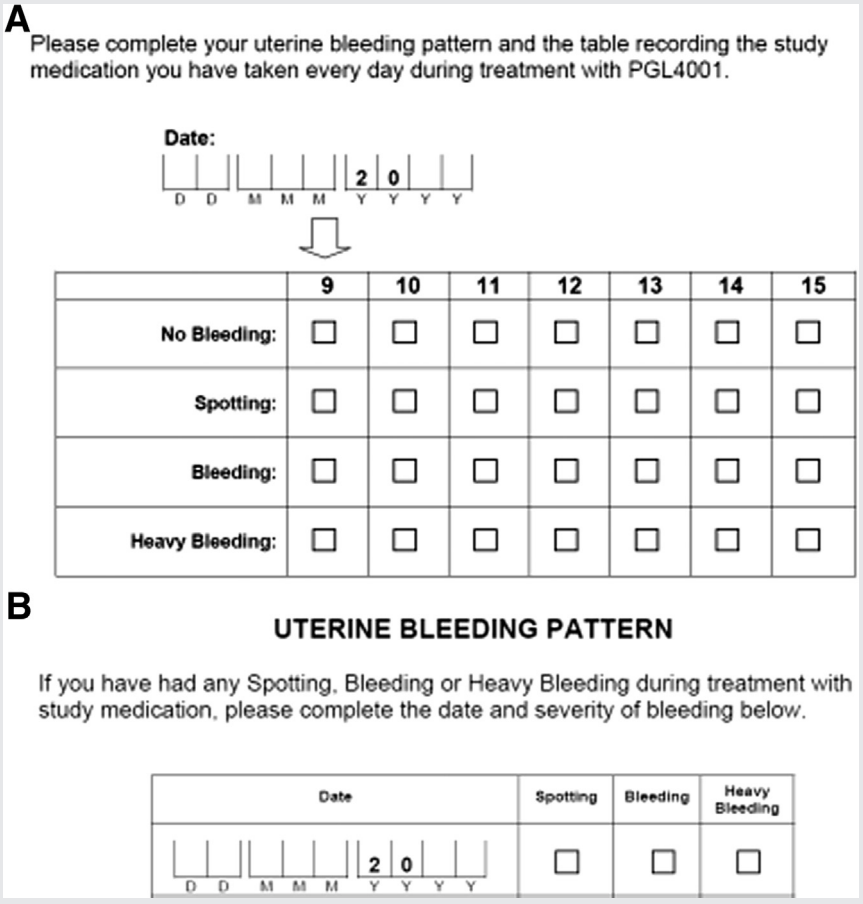
SUPPLEMENTAL FIGURE 3



Patient disposition for participants entering PEARL III and PEARL III extension, including details for NETA/placebo treatment groups. [a]One woman was treated correctly for treatment course 1 but received only placebo medication (no UPA) in error for treatment course 2. [b]Includes one woman who was withdrawn owing to an adverse event occurring in an off-treatment period.

Donnez. Long-term treatment of uterine fibroids. Fertil Steril 2014.

SUPPLEMENTAL FIGURE 4



Assessment of uterine bleeding. (A) Semiquantitative bleeding scale used in PEARL III. (B) Semiquantitative bleeding scale used in PEARL III extension. (C) Example of a completed PBAC showing a score of 320 (equivalent to a menstrual blood loss of approximately 250 mL).

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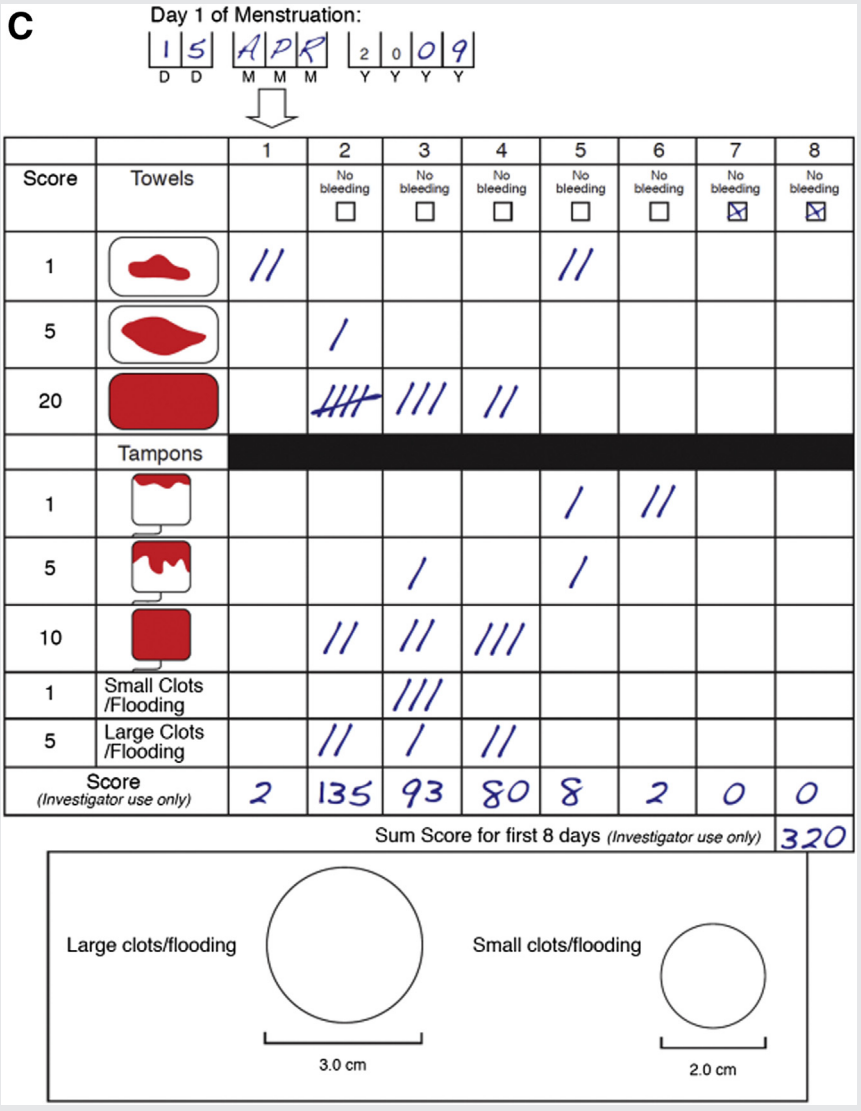
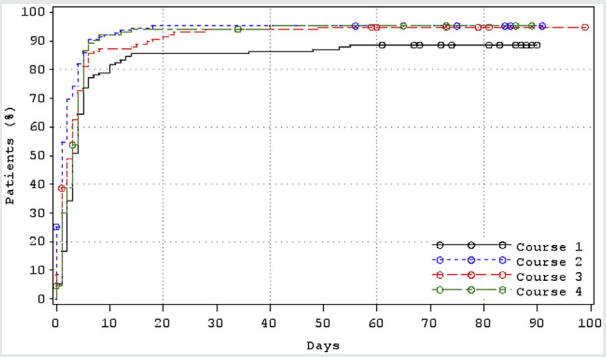
SUPPLEMENTAL FIGURE 4 Continued



Donnez. Long-term treatment of uterine fibroids. Fertil Steril 2014.

SUPPLEMENTAL FIGURE 5



Time to spotting/no bleeding (PEARL III extension full analysis set). Time to spotting/no bleeding was defined as the first day for which there was subsequently only spotting or no bleeding for longer than 35 days to the end of UPA treatment within each treatment course, assessed using the patient diary data from the date of the first dose of UPA (day 0, which was to be within the first 4 days of the start of menstruation for treatment courses 1 and 2 and on the first day of menstruation for treatment courses 3 and 4). Circles denote censored observation (i.e., a woman had a subsequent interval of 35 days or less up to the end of UPA treatment for which only spotting or no bleeding was observed).

Donnez. Long-term treatment of uterine fibroids. Fertil Steril 2014.

SUPPLEMENTAL TABLE 1

Key exclusion criteria.

Previous uterine surgery including endometrial ablation or uterine artery embolization.
History of or current uterus, cervix, ovarian, or breast cancer.
Significant finding on Papanikolaou test (PAP) smear within the past 12 months.
Endometrium hyperplasia or adenocarcinoma within the past 6 months or similar lesions in the screening biopsy. In case of biopsies older than 6 months, these had to be repeated.
Large uterine polyp (>2 cm).
Calcified fibroids and/or a calcified uterus.
Severe coagulation disorder.
One or more ovarian cysts ≥4 cm diagnosed by ultrasound.
History of treatment for fibroid with an SPRM, including UPA.
Treatments with progestins (systemic or progestin-releasing intrauterine system), oral contraceptive, acetylsalicylic acid, mefenamic acid, anticoagulants such as cumarins and/or antifibrinolytic drugs such as tranexamic acid, P antagonists, systemic glucocorticoid treatments and/or systemic depot glucocorticoid, treatments that contain PgP substrate (digoxin, fexofenadine) or contain moderate or potent inhibitors or inducers of CYP3A4.

Donnez. Long-term treatment of uterine fibroids. Fertil Steril 2014.

SUPPLEMENTAL TABLE 2

Efficacy results for first treatment course (PEARL III open-label set; n = 209).

Assessment	n	Result[a]
Amenorrhea		
No. of women in amenorrhea (%)	209	164 (78.5)
95% CI, %	209	72.4, 83.5
Spotting/no bleeding		
No. of women with spotting or no bleeding (%)	209	181 (86.6)
95% CI	209	81.3, 90.6
Total volume of three largest fibroids[b]		
% Change from baseline, median (IQR)	194	−45.1 (−66.1, −24.9)
Total reduction ≥25%, n (%)	194	145 (74.7)
Total reduction ≥50%, n (%)	194	86 (44.3)
Uterine volume		
% Change from baseline, median (IQR)	201	−28.9 (−45.5, −8.4)
Reduction ≥25%, n (%)	201	109 (54.2)
Assessment of pain		
SF-MPQ[c]		
End of week 4 actual, median (IQR)	204	2.0 (0.0, 4.0)
End of week 4 change from baseline, median (IQR)	202	−5.0 (−12.0, −1.0)
End of week 8 actual, median (IQR)	198	0.0 (0.0, 2.0)
End of week 8 change from baseline, median (IQR)	196	−6.0 (−14.0, −1.6)
End of course 1 actual, median (IQR)	200	1.0 (0.0, 3.0)
Course 1 change from baseline, median (IQR)	198	−6.0 (−14.0, −2.0)
Visual analog scale (VAS)[d]		
End of week 4 actual, median (IQR)	204	8.0 (0.0, 28.0)
End of week 4 change from baseline, median (IQR)	204	−21.0 (−39.0, −2.0)
End of week 8 actual, median (IQR)	202	2.0 (0.0, 12.0)
End of week 8 change from baseline, median (IQR)	202	−26.0 (−54.0, −7.0)
Course 1 actual, median (IQR)	200	1.0 (0.0, 12.0)
Course 1 change from baseline, median (IQR)	200	−24.5 (−54.0, −6.0)
UFS-QoL questionnaire[e]		
Symptom severity		
Actual, mean ± SD	196	14.5 ± 15.5
Change from baseline, mean ± SD	194	−33.3 ± 21.5
Health-Related QoL total score		
Actual, mean ± SD	201	86.2 ± 15.6
Change from baseline, mean ± SD	200	29.2 ± 22.4
EQ-5D questionnaire		
Mobility (women with problems), n (%)	201	10 (5.0)
Self-care (women with problems), n (%)	201	0 (0.0)
Usual activities (women with problems), n (%)	200	12 (6.0)
Pain/discomfort (women with moderate/extreme symptoms), n (%)	200	60 (30.0)
Anxiety/depression (women with moderate/extreme symptoms), n (%)	201	84 (41.8)
VAS (health state)[f]		
Actual, mean ± SD	200	76.8 ± 17.6
Change from baseline, mean ± SD	200	9.6 ± 23.3

Donnez. Long-term treatment of uterine fibroids. Fertil Steril 2014.

SUPPLEMENTAL TABLE 2

Continued.

Note: n = Number of women with nonmissing observations.

[a] Assessments were made at end of a 13-week treatment course of UPA and before 10-day treatment course of NETA/placebo, except for the SF-MPQ, which was also assessed after 4 and 8 weeks of treatment.

[b] The same three fibroids identified at screening were followed throughout the study.

[c] Scores on the SF-MPQ range from 0 to 45, with higher scores indicating more severe pain.

[d] Scores on the VAS of the SF-MPQ range from 0 to 100, with higher scores indicating more severe pain.

[e] Scores on the VAS of the EQ-5D range from 0 to 100, with higher scores indicating a better health state.

[f] On the UFS-QoL questionnaire, scores for symptom severity range from 0 to 100, with higher scores indicating increased severity. Total scores for health-related QoL range from 0 to 100, with higher scores indicating a better QoL.

Donnez. Long-term treatment of uterine fibroids. Fertil Steril 2014.

SUPPLEMENTAL TABLE 3

Summary of PBAC at the start of treatment course 1 and PBAC and timing of first menstruation after each treatment course.

	Total	UPA then placebo	UPA then NETA	*P* value[a]
PEARL III (double-blind set)	n = 201	n = 103	n = 98	
PBAC score (days 1–8 of first menses)[b]				
Postscreening, median (IQR)	216 (126, 376)	218 (126, 344)	206 (131, 422)	
Post-treatment course 1	n = 194	n = 99	n = 95	
Actual, median (IQR)	98 (36, 211)	123 (51, 248)	75 (27, 179)	
Change, median (IQR)	−92 (−220, 23)	−69 (−167, 40)	−122 (−299, −9)	.01
Time to return to menstruation, days[c]				
Post-treatment course 1	n = 196	n = 101	n = 95	
Median (IQR)	18 (14, 26)	25 (20, 29)	14 (13, 15)	< .0001
PEARL III extension (full analysis set)	n = 132	n = 69	n = 63	
PBAC score (days 1–8 of first menses)[b]				
Post-screening, median (IQR)	235 (142, 397)	228 (142, 139)	257 (140, 498)	
Post-treatment course 1	n = 131	n = 69	n = 62	
Actual, median (IQR)	94 (31, 210)	123 (53, 233)	59 (21, 155)	
Change, median (IQR)	−120 (−264, 5)	−92 (−171, 25)	−144 (−367, −42)	.006
Post-treatment course 2	n = 123	n = 65	n = 58	
Actual, median (IQR)	64 (20, 168)	84 (18, 226)	54 (21, 103)	
Change, median (IQR)	−150 (−255, −55)	−127 (−211, −14)	−171 (−372, −71)	.01
Post-treatment course 3	n = 114	n = 58	n = 56	
Actual, median (IQR)	42 (14, 138)	75 (22, 191)	28 (9, 66)	
Change, median (IQR)	−131 (−311, −59)	−103 (−186, −36)	−224 (−461, −104)	< .0003
Post-treatment course 4	n = 89	n = 49	n = 40	
Actual, median (IQR)	31 (11, 100)	55 (22, 136)	13 (6, 48)	
Change, median (IQR)	−120 (−255, −45)	−97 (−184, −31)	−166 (−356, −74)	.02
Time to return to menstruation, days[c]				
Post-treatment course 1	n = 131	n = 69	n = 62	
Median (IQR)	18 (14, 27)	25 (20, 30)	14 (13, 15)	< .0001
Post-treatment course 2	n = 125	n = 66	n = 59	
Median (IQR)	18 (14, 27)	26 (21, 34)	14 (13, 17)	< .0001
Post-treatment course 3	n = 116	n = 60	n = 56	
Median (IQR)	21 (14, 31)	30 (24, 36)	14 (13, 17)	< .0001
Post-treatment course 4	n = 99	n = 53	n = 46	
Median (IQR)	22 (15, 34)	30 (23, 35)	15 (14, 18)	< .0001

[a] Tests comparing NETA to placebo were conducted using the Wilcoxon rank sum test.
[b] PBAC score postscreening assessment measured during days 1–8 at start of UPA treatment course 1. Score post-treatment course assessments measured during days 1–8 of first menstruation after the end of the respective treatment course.
[c] Excludes women in whom surgery was performed before return of menstruation or women discontinued before return of menstruation.

Donnez. Long-term treatment of uterine fibroids. Fertil Steril 2014.

SUPPLEMENTAL TABLE 4

Selected efficacy results for participants not entering/entering the PEARL III extension study.

	Did not enter extension	Entered extension	Difference	Statistics[a]
Amenorrhea, n/N (%)[b]	59/77 (76.6)	105/132 (79.5)	(2.9)	.73
95% CI, %	66.0, 84.7	71.9, 85.5	−8.8, 14.6	
Spotting or no bleeding, n/N (%)[b]	64/77 (83.1)	117/132 (88.6)	(5.5)	.30
95% CI, %	73.2, 89.9	82.1, 93.0	−4.4, 15.5	
Total volume of three largest fibroids[c]	n = 64	n = 130		
% Change from baseline	−38.5	−49.9	−12.1	.01
95% CI, %	−47.8, −29.0	−56.7, −42.5	−22.2, −2.7	
Uterine volume	n = 69	n = 132		
% Change from baseline	−27.0	−29.8	−1.4	.79
95% CI, %	−33.9, −14.5	−35.3, −22.6	−10.1, 7.5	
Assessment of pain				
VAS[d]	n = 68	n = 132		
Change from baseline	−27.5	−23.5	−3.0	.53
95% CI, %	−36.0, −13.0	−34.0, −17.0	−12.0, 6.0	
UFS-QoL questionnaire[e]				
Symptom severity	n = 65	n = 129		
Change from baseline	−28.4	−35.8		
Least square mean	−30.6	−34.7	−4.1	.08
95% CI, %	−34.3, −26.8	−37.3, −32.0	−8.7, 0.5	
Health-related QoL total score	n = 69	n = 131		
Change from baseline	22.2	32.8		
Least square mean	25.3	31.2	5.9	.009
95% CI, %	21.7, 28.8	28.6, 33.8	1.5, 10.3	

[a] Fisher's exact test was used for amenorrhea and spotting or no bleeding; Wilcoxon rank sum test was used for total volume of three largest fibroids, uterine volume, assessment of pain (medians reported), and analysis of covariance for the UFS-QoL questionnaire (means reported).
[b] Amenorrhea (and spotting or no bleeding) assessed while under UPA treatment. For remaining results, data were collected at the end of UPA treatment.
[c] The same three fibroids identified at screening were followed throughout the study.
[d] Scores on VAS range from 0 to 100, with higher scores indicating more severe pain.
[e] On the UFS-QoL questionnaire, scores for symptom severity range from 0 to 100, with higher scores indicating increased severity. Total scores for health-related QoL range from 0 to 100, with higher scores indicating a better QoL.

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SUPPLEMENTAL TABLE 5

Adverse events (PEARL III safety set; n = 209).[a]

Adverse event	No. of women (%)
SAEs	
At least one SAE	2 (1.0)
Any SAE during UPA treatment	0
Any SAE during NETA/Placebo treatment	0
Any SAE off treatment	2 (1.0)[b]
Menometrorrhagia	1 (0.5)
Uterine hemorrhage	1 (0.5)
Breast cancer	1 (0.5)[c]
Adverse events[d]	
Leading to study withdrawal[e]	1 (0.5)
At least one event	120 (57.4)
Headache	34 (16.3)
Nasopharyngitis	14 (6.7)
Abdominal pain (including upper/lower)	11 (5.3)
Hot flashes	10 (4.8)
Fatigue	9 (4.3)
Nausea	8 (3.8)
Vertigo	8 (3.8)
Breast discomfort/breast pain/breast tenderness	8 (3.8)
Pelvic pain	8 (3.8)

[a] All adverse events that occurred during UPA treatment in at least 3% of women overall and all SAEs are included.
[b] One woman had two off-treatment SAEs.
[c] A 46-year-old woman was diagnosed with a lobular breast cancer 2 months after the end of treatment (T1, grade II).
[d] Adverse events with onset on or after the first dose of UPA and before the first dose of NETA/placebo within each treatment course or up to and including 7 days after the last dose of UPA if NETA/placebo was never started.
[e] In addition, another adverse event that occurred when a woman was not receiving UPA led to study withdrawal.

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SUPPLEMENTAL TABLE 6

Summary of other safety assessments (PEARL III safety set; n = 209).

Assessment[a]	n	Result
Serum E_2, pg/mL		
Screening, median (IQR)	205	120.0 (77, 184)
Course 1, median (IQR)	180	55.0 (41, 84)
ACTH, pg/mL		
Screening, median (IQR)	196	13.3 (9.3, 19.8)
Course 1, median (IQR)	177	13.2 (9.2, 17.1)
TSH, mIU/L		
Screening, median (IQR)	205	1.36 (0.96, 1.96)
Course 1, median (IQR)	181	1.49 (1.00, 2.00)
PRL, ng/mL		
Screening, median (IQR)	205	11.4 (8.2, 18.2)
Course 1, median (IQR)	180	7.9 (5.5, 11.7)
Total cholesterol, mmol/L		
Screening, median (IQR)	205	5.06 (4.48, 5.60)
Course 1, median (IQR)	180	5.25 (4.71, 5.82)
Second menstrual bleed post-treatment, median (IQR)	123	4.89 (4.41, 5.47)
3-Month follow-up, median (IQR)	56	5.16 (4.44, 5.93)
HDL, mmol/L		
Screening, median (IQR)	205	1.61 (1.43, 1.91)
Course 1, median (IQR)	180	1.64 (1.44, 1.89)
Second menstrual bleed post-treatment, median (IQR)	123	1.56 (1.31, 1.81)
3-Month follow-up, median (IQR)	56	1.72 (1.46, 1.92)
LDL, mmol/L		
Screening, median (IQR)	203	2.81 (2.40, 3.39)
Course 1, median (IQR)	178	2.97 (2.55, 3.54)
Second menstrual bleed post-treatment, median (IQR)	121	2.72 (2.30, 3.07)
3-Month follow-up, median (IQR)	56	2.73 (2.19, 3.53)
Endometrial thickness, mm		
Screening, mean ± SD	202	8.7 ± 3.7
≤4 mm, n (%)		14 (6.9)
>4 to ≤16 mm, n (%)		185 (91.6)
>16 mm, n (%)		3 (1.5)
Course 1, mean ± SD	198	9.2 ± 4.6
≤4 mm, n (%)		23 (11.6)
>4 to ≤16 mm, n (%)		157 (79.3)
>16 mm, n (%)		18 (9.1)
2 Weeks after first menstrual bleed post-treatment, mean ± SD	181	8.9 ± 4.1
≤4 mm, n (%)		19 (10.5)
>4 to ≤16 mm, n (%)		150 (82.9)
>16 mm, n (%)		12 (6.6)
3-Month follow-up, mean ± SD	48	7.6 ± 3.4
≤4 mm, n (%)		9 (18.8)
>4 to ≤16 mm, n (%)		39 (81.3)
>16 mm, n (%)		0
Systolic blood pressure, mmHg		
Baseline, mean ± SD	209	121.4 ± 13.8
End of week 4, mean ± SD	207	119.7 ± 13.1
End of week 8, mean ± SD	203	119.7 ± 13.7
Course 1, mean ± SD	202	120.2 ± 13.7
2 Weeks after first menstrual bleed post-treatment, mean ± SD	191	121.9 ± 12.3

Donnez. Long-term treatment of uterine fibroids. Fertil Steril 2014.

SUPPLEMENTAL TABLE 6

Continued.

Assessment[a]	n	Result
Second menstrual bleed post-treatment, mean ± SD	132	119.8 ± 13.2
3-Month follow-up, mean ± SD	57	120.4 ± 13.6
Diastolic blood pressure, mmHg		
Baseline, mean ± SD	209	74.4 ± 9.8
End of week 4, mean ± SD	207	73.4 ± 9.9
End of week 8, mean ± SD	203	74.0 ± 10.0
Course 1, mean ± SD	202	74.2 ± 9.9
2 Weeks after first menstrual bleed post-treatment, mean ± SD	191	74.9 ± 9.5
Second menstrual bleed post-treatment, mean ± SD	132	73.6 ± 9.4
3-Month follow-up, mean ± SD	57	74.5 ± 10.8
Pulse rate, bpm		
Baseline, mean ± SD	209	73.9 ± 10.7
End of week 4, mean ± SD	207	72.6 ± 9.3
End of week 8, mean ± SD	203	72.7 ± 9.3
Course 1, mean ± SD	201	72.1 ± 9.4
2 Weeks after first menstrual bleed post-treatment, mean ± SD	191	72.8 ± 9.5
Second menstrual bleed post-treatment, mean ± SD	132	72.4 ± 10.4
3-Month follow-up, mean ± SD	56	72.2 ± 10.8
Weight, kg		
Baseline, mean ± SD	209	69.0 ± 12.8
Course 1, mean ± SD	202	68.5 ± 12.8
Second menstrual bleed post-treatment, mean ± SD	132	68.2 ± 13.2
3-Month follow-up, mean ± SD	58	70.2 ± 11.7

Note: n = Number of women with nonmissing observations.
[a] Course 1 data were collected at the end of UPA treatment. Second menstrual bleed post-treatment data were collected for those entering the extension; 3-month follow-up data were collected for those not entering the extension.

Donnez. Long-term treatment of uterine fibroids. Fertil Steril 2014.

SUPPLEMENTAL TABLE 7

Summary of pathologist consensus of nonphysiological histological features in the endometrium.

	Total	UPA then Placebo	UPA then NETA
PEARL III	n = 209	n = 103	n = 98
Screening	n = 171	n = 85	n = 80
No. of women (%)	18 (10.5)	7 (8.2)	11 (13.8)
2 Weeks after first menstrual bleed post-treatment	n = 176	n = 92	n = 84
No. of women (%)	45 (25.6)	26 (28.3)	19 (22.6)
PEARL III extension	n = 132	n = 69	n = 63
Screening	n = 105	n = 56	n = 49
No. of women (%)	11 (10.5)	4 (7.1)	7 (14.3)
2 Weeks after first menstrual bleed post-treatment course 1	n = 122	n = 65	n = 57
No. of women (%)	35 (28.7)	20 (30.8)	15 (26.3)
2 Weeks after first menstrual bleed post-treatment course 4	n = 87	n = 47	n = 40
No. of women (%)	22 (25.3)[a]	11 (23.4)	11 (27.5)

Note: n = Number of women with nonmissing observations.

[a] Of the 22 women diagnosed with a consensus of nonphysiological histological features 2 weeks after first menstrual bleed post-treatment course 4, 15 (7 placebo, 8 NETA) women had biopsies at 3-month follow-up. Of these, three (1 placebo and 2 NETA) women were diagnosed with nonphysiological histological features at this follow-up visit.

Donnez. Long-term treatment of uterine fibroids. Fertil Steril 2014.

SUPPLEMENTAL TABLE 8

Women in amenorrhea at the end of each treatment course by total volume of a reduction ≥25% of the three largest fibroids.

Treatment course	Fibroid volume reduction ≥25%[a]	Total	Amenorrhea, n (%)
Course 1	Yes	101	82 (81.2)
	No	29	22 (75.9)
	Total[b]	130	104 (80.0)
Course 2	Yes	95	88 (92.6)
	No	24	19 (79.2)
	Total[b]	119	107 (89.9)
Course 3	Yes	83	74 (89.2)
	No	23	21 (91.3)
	Total[b]	106	95 (89.6)
Course 4	Yes	79	75 (94.9)
	No	17	14 (82.4)
	Total[b]	96	89 (92.7)

[a] Fibroid volume reduction assessed using total volume of the three largest fibroids assessed during the screening period before the first treatment course. The same three fibroids identified at screening were followed throughout the study. Course 1 and 4 data were collected at the end of UPA treatment; course 2 and 3 data were collected after first menstrual bleed after UPA treatment and subsequent NETA/placebo treatment.

[b] Overall totals for each treatment course are the number of women receiving UPA in each treatment course who did not have surgery performed during or before the end of each treatment course and who have a nonmissing amenorrhea assessment and nonmissing fibroid volume reduction assessment for the treatment course in question.

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SUPPLEMENTAL TABLE 9

Summary of other safety assessments (PEARL III extension safety set; n = 132)

Assessment[a]	n	Result
Serum E_2, pg/mL		
Screening, median (IQR)	131	120.0 (76.0, 185.0)
Course 1, median (IQR)	112	54.0 (38.5, 81.0)
Course 2, median (IQR)	119	129.0 (62.0, 194.0)
Course 4, median (IQR)	95	43.0 (27.0, 61.0)
3-Month follow-up, median (IQR)	96	96.5 (66.5, 173.0)
ACTH, pg/mL		
Screening, median (IQR)	126	13.0 (9.3, 19.3)
Course 1, median (IQR)	117	12.7 (9.7, 16.9)
Course 2, median (IQR)	103	12.6 (8.3, 17.3)
Course 4, median (IQR)	86	12.5 (8.1, 16.3)
3-Month follow-up, median (IQR)	89	13.2 (8.9, 20.9)
TSH, mIU/L		
Screening, median (IQR)	131	1.31 (0.94, 1.83)
Course 1, median (IQR)	113	1.41 (0.93, 2.00)
Course 2, median (IQR)	119	1.35 (0.92, 1.88)
Course 4, median (IQR)	95	1.39 (0.84, 2.16)
3-Month follow-up, median (IQR)	96	1.33 (0.90, 1.85)
PRL, ng/mL		
Screening, median (IQR)	131	11.3 (8.9, 18.5)
Course 1, median (IQR)	112	7.55 (5.45, 11.35)
Course 2, median (IQR)	118	8.85 (6.30, 12.90)
Course 4, median (IQR)	95	6.90 (5.10, 11.60)
3-Month follow-up, median (IQR)	96	9.35 (7.35, 15.35)
Total cholesterol, mmol/L		
Screening, median (IQR)	131	5.00 (4.50, 5.58)
Course 1, median (IQR)	112	5.25 (4.93, 5.78)
Course 2, median (IQR)	119	4.97 (4.57, 5.49)
Course 4, median (IQR)	94	5.33 (4.93, 5.85)
3-Month follow-up, median (IQR)	96	5.17 (4.73, 5.69)
HDL, mmol/L		
Screening, median (IQR)	131	1.61 (1.43, 1.88)
Course 1, median (IQR)	112	1.65 (1.41, 1.92)
Course 2, median (IQR)	119	1.59 (1.40, 1.90)
Course 4, median (IQR)	94	1.60 (1.40, 1.87)
3-Month follow-up, median (IQR)	96	1.62 (1.41, 1.92)
LDL, mmol/L		
Screening, median (IQR)	129	2.81 (2.40, 3.38)
Course 1, median (IQR)	110	3.01 (2.60, 3.50)
Course 2, median (IQR)	117	2.77 (2.41, 3.26)
Course 4, median (IQR)	94	3.04 (2.58, 3.62)
3-Month follow-up, median (IQR)	96	2.95 (2.52, 3.56)
Endometrial thickness, mm		
Screening, mean ± SD	129	9.3 ± 4.0
≤4 mm, n (%)		7 (5.4)
>4 to ≤16 mm, n (%)		119 (92.2)
>16 mm, n (%)		3 (2.3)
Course 1, mean ± SD	130	9.4 ± 4.5
≤4 mm, n (%)		13 (10.0)
>4 to ≤16 mm, n (%)		107 (82.3)
>16 mm, n (%)		10 (7.7)
Course 2, mean ± SD	120	8.8 ± 3.8
≤4 mm, n (%)		15 (12.5)
>4 to ≤16 mm, n (%)		101 (84.2)
>16 mm, n (%)		4 (3.3)
Course 3, mean ± SD	107	8.0 ± 3.4
≤4 mm, n (%)		15 (14.0)
>4 to ≤16 mm, n (%)		91 (85.0)
>16 mm, n (%)		1 (0.9)

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SUPPLEMENTAL TABLE 9

Continued.

Assessment[a]	n	Result
Course 4, mean ± SD	95	7.5 ± 3.4
≤4 mm, n (%)		17 (17.9)
>4 to ≤16 mm, n (%)		77 (81.1)
>16 mm, n (%)		1 (1.1)
3-Month follow-up, mean ± SD	97	8.9 ± 3.2
≤4 mm, n (%)		6 (6.2)
>4 to ≤16 mm, n (%)		89 (91.8)
>16 mm, n (%)		2 (2.1)
Systolic blood pressure, mmHg		
Baseline, mean ± SD	132	122.2 ± 14.1
Course 1, mean ± SD	132	120.5 ± 13.6
Course 2, mean ± SD	121	120.4 ± 13.7
Course 3, mean ± SD	109	120.3 ± 11.4
Course 4, mean ± SD	96	120.7 ± 13.3
3-Month follow-up, mean ± SD	99	119.5 ± 11.0
Diastolic blood pressure, mmHg		
Baseline, mean ± SD	132	74.2 ± 9.3
Course 1, mean ± SD	132	74.4 ± 9.7
Course 2, mean ± SD	121	74.7 ± 10.3
Course 3, mean ± SD	109	73.6 ± 8.8
Course 4, mean ± SD	96	74.4 ± 8.1
3-Month follow-up, mean ± SD	99	73.5 ± 9.2
Pulse rate, bpm		
Baseline, mean ± SD	132	73.8 ± 10.7
Course 1, mean ± SD	132	72.5 ± 9.5
Course 2, mean ± SD	121	73.8 ± 10.5
Course 3, mean ± SD	109	73.3 ± 9.5
Course 4, mean ± SD	96	72.2 ± 8.7
3-Month follow-up, mean ± SD	99	72.9 ± 9.5
Weight, kg		
Baseline, mean ± SD	132	68.7 ± 13.6
Course 1, mean ± SD	132	67.8 ± 13.3
Course 2, mean ± SD	121	67.3 ± 12.6
Course 3, mean ± SD	109	67.5 ± 12.7
Course 4, mean ± SD	96	67.4 ± 12.6
3-Month follow-up, mean ± SD	99	67.8 ± 13.3

Note: n = Number of women with nonmissing observations.
[a] Course 1 and 4 data were collected at the end of UPA treatment; course 2 and 3 data were collected after first menstrual bleed after UPA treatment and subsequent NETA/placebo treatment.

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