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Phase III long-term study to evaluate the efficacy and safety of ulipristal acetate in Japanese patients with uterine fibroids

Yutaka Osuga[1], Yasuaki Nakano[2], Yuji Yamauchi[2] and Hitoshi Murakawa[2]

[1]*Department of Gynecologic Surgery, The University of Tokyo Hospital, Tokyo, Japan*
[2]*Clinical Development Department, ASKA Pharmaceutical Co., Ltd., Tokyo, Japan*

Abstract

Aim: To assess the efficacy and safety of long-term intermittent administration of 10-mg ulipristal acetate (UPA) for symptomatic uterine fibroids in Japanese women.

Methods: Open-label, noncomparative study (Japan Primary Registries Network identifier: JapicCTI-173737) conducted at 32 gynecological centers (November 2017–December 2019). Premenopausal women diagnosed with uterine fibroids associated with heavy menstrual bleeding received three 12-week courses of 10-mg UPA once daily. Amenorrhea, fibroid volume, endometrial histology, and safety were assessed.

Results: Of 155 patients enrolled, 140 received ≥1 dose of UPA and were analyzed. Across all courses, the rates of patients with amenorrhea for 35 days were >90%, and >99% of patients achieved uterine bleeding normalization. Median time to amenorrhea after each course started was 4–5 days; menstruation returned after treatment within a median of 25–27 days. Mean changes in fibroid volume from baseline were −21.5%, −31.4%, and −35.0% for Courses 1, 2, and 3, respectively. Patients experienced sustained improvements in anemia, pain, and quality of life during treatment. Most adverse events were mild/moderate in severity and decreased in frequency with each course. Seven serious adverse events (six patients) were reported; anemia, embolic cerebral infarction, and pituitary apoplexy (one patient each) were considered UPA-related. Non-physiological changes in endometrial histology were transient and benign. No safety concerns were detected in hormone concentrations or liver function tests.

Conclusions: Long-term administration of 10-mg UPA is effective for reducing symptoms associated with uterine fibroids in Japanese women. UPA was well tolerated and few safety concerns were reported.

Key words: uterine fibroids, leiomyoma, long-term care, menorrhagia, ulipristal acetate.

Introduction

Uterine fibroids are a common and mostly asymptomatic gynecological condition that typically occurs in premenopausal women.[1,2] Approximately 30% of women with uterine fibroids experience severe symptoms, including heavy menstrual bleeding and pelvic pain and pressure,[1] which typically result in anemia, chronic fatigue, and significantly impaired quality of life (QOL).[3–5] When symptoms are severe, uterine fibroids require medical or surgical intervention and incur substantial economic burden arising from decreased productivity and health care costs.[1,5] While hysterectomy is the mainstay of treatment,[1] conservative medical treatment is considered for some women and to reduce fibroid volume and improve menstrual

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Correspondence: Yasuaki Nakano, Clinical Development Department, ASKA Pharmaceutical Co., Ltd. 5-1, 2-Chome, Shibaura, Minato-ku, Tokyo 108-8532, Japan.
Email: nakano-y2@aska-pharma.co.jp

bleeding before surgery.[6] Gonadotrophin-releasing hormone (GnRH) agonists and antagonists are used for treatment of uterine fibroids, but because of estrogen suppression, patients can experience unwanted adverse effects associated with medical induction of menopause, including loss of bone mineral density. Hence consecutive administration of GnRH agonists and antagonists is typically limited to 6 months.[7]

Ulipristal acetate (UPA) is a selective progesterone receptor modulator (SPRM) that antagonizes the progesterone receptor and suppresses uterine bleeding, without suppressing ovarian estrogen,[8–10] and is thought to have a direct effect on fibroid volume by inhibiting fibroid cell proliferation and inducing apoptosis.[8,11] The efficacy and safety of UPA have been evaluated in the PGL4001 UPA Efficacy Assessment in Reduction of symptoms due to uterine Leiomyoma (PEARL) trials conducted in Europe.[8,12,13] Findings from these trials demonstrated that the 5- and 10-mg doses of UPA, administered daily, were effective as preoperative treatment of symptomatic uterine fibroids for up to 3 months.[8,12] In these studies, 73%–89% of patients had amenorrhea, and fibroid volume decreased between 12% and 42%. The 10-mg dose was also shown to be effective during four intermittent 12-week courses, with amenorrhea rates of 80%–90% and fibroid volume decreases of 50%–72%.[13] Although findings from these trials showed UPA to be well tolerated with no major safety concerns,[14] several cases of severe liver injury and hepatic failure have been reported as part of postmarketing surveillance among >900 000 women who used 5-mg UPA for treatment of uterine fibroids in Europe since 2012.[14,15] Because of these hepatic injuries, the European Medicines Agency (EMA) recommends restricting the use of 5-mg UPA.[16]

Two randomized studies have assessed the efficacy and safety of UPA in Japanese women: a 12-week dose-finding study[17] and a 12-week active-controlled study.[18] However, no studies have assessed the long-term efficacy and safety of UPA in Japanese women. In the dose-finding study, a significant dose response was observed in the rates of amenorrhea and bleeding control, time to amenorrhea, and reductions in uterine fibroid volume across 2.5–10-mg UPA administered daily. As there was no apparent difference in safety among the doses, the recommended dose of UPA for Japanese patients was determined to be 10 mg. The therapeutic effect of 10-mg UPA on heavy menstrual bleeding was shown to be similar to that of the GnRH analog, leuprorelin, in Japanese patients with symptomatic uterine fibroids.[18] The objective of the current study was to assess the efficacy and safety of long-term intermittent administration of 10-mg UPA for treatment of symptomatic uterine fibroids in Japanese women.

Methods

Study design

This phase III, long-term, open-label, multicenter study in Japanese patients with uterine fibroids (Japan Primary Registries Network identifier: JapicCTI-173737) was conducted at 32 Japanese gynecological centers between November 2017 and December 2019. The protocol and informed consent forms were reviewed and approved by the sponsor and the applicable institutional review boards/ethics committees with respect to scientific content and compliance with the Japanese Ethical Guidelines for Clinical Studies and the Declaration of Helsinki. All patients provided written informed consent.

Study population

Eligible patients were premenopausal Japanese women aged between 20 and 50 years who were diagnosed with uterine fibroids associated with heavy menstrual bleeding, had a regular menstrual cycle of 22–35 days, with a pictorial blood loss assessment chart (PBAC) score >100 during the first 8 days of menses and at least one noncalcified fibroid ≥3 cm in diameter in the pretreatment period. Patients were excluded if they had a history of uterine surgery (including uterine artery embolization) on the fibroids of interest and/or a history of intrauterine curettage or microwave endometrial ablation within the previous 6 months. Patients were also excluded as follows: history of malignant tumor within the previous 5 years; history of treatment with SPRM (including UPA); endometrial polyps >2 cm; ovarian cysts ≥4 cm; marked metrorrhagia; hemoglobinopathy (including sickle cell anemia and thalassemia) or severe coagulation disorder; significant endometrial histological abnormalities (including endometrial hyperplasia); pregnancy or breastfeeding; use of particular medications, including GnRH derivatives, sex hormones, oral contraceptives, anticoagulants, antiplatelets, antifibrinolytics, and systemic corticosteroids; abnormal hepatic function during the pretreatment observation period, defined as aspartate aminotransferase (AST), alanine aminotransferase

(ALT), gamma-glutamyl transferase (γ-GT), alkaline phosphatase (ALP), or total bilirubin more than twice the upper limit of the reference range; and the possibility of use of moderate or potent cytochrome P450 (CYP) 3A4 inhibitors or potent CYP3A4 inducers.

Intervention and treatment protocol

Following pretreatment (including screening), patients received three 12-week courses of 10-mg UPA once daily, with each course followed by an off-treatment period. For Course 3, the off-treatment period comprised the end-of-study follow-up, from Week 13 to Week 24 (84 days) (Figure S1). For Course 1, UPA was initiated in the first 7 days of menstruation. For Courses 2 and 3, UPA was initiated within 7 days after the start of the second menstruation following the end of the previous treatment course (during the off-treatment period).

Efficacy outcome measures

The primary efficacy endpoint was the rate of patients with amenorrhea for 35 days (the 35-day amenorrhea rate), between Days 50 and 84 of each treatment course, defined as the percentage of patients with a PBAC score ≤2 for 35 continuous days. For assessment of uterine bleeding, patients recorded their bleeding pattern using the PBAC in an electronic daily diary during the study period.[19]

Other efficacy endpoints, assessed for each course, included the following: the rate of patients with amenorrhea for 56 days, between Days 29 and 84; the rate of uterine bleeding normalization, defined as the percentage of patients with a PBAC score <75 for 35 days, between Days 50 and 84; the percentage change in PBAC score from baseline during the menstrual period at each time point (pretreatment observation period, treatment initiation, off-treatment period, and follow-up period); time to amenorrhea; time from end of treatment to recovery of menstruation; percentage change from baseline (at screening) in the volume of the three largest fibroids and uterus, measured using transvaginal ultrasonography by the same (if possible) trained operator, at Week 12 of each course and at Week 24 of Course 3 (during follow-up); change from the start of each course in hemoglobin (g/dL); change from baseline (at start of Course 1) in pain, assessed using a visual analog scale (VAS; pain scores ranged from 0 [no pain] to 100 [worst possible pain]); and change from baseline (at start of Course 1) in the Uterine Fibroid System and Health-Related Quality of Life (HRQOL) questionnaire (UFS-QOL), which comprises a symptom severity score (lower scores indicate fewer symptoms) and a HRQOL score (higher scores indicate better QOL).[3]

Safety outcome measures

The severity and relationship with UPA of treatment-emergent adverse events (AEs) were assessed by the investigators. Other safety outcomes included the following: endometrial thickness, measured using transvaginal ultrasonography; and endocrinology, hematology, bone turnover markers (serum procollagen type I N-terminal propeptide, serum bone alkaline phosphatase, urine deoxypyridinoline, and urine crosslinked N-telopeptide of type I collagen) and biochemistry measures. Endometrial biopsies were evaluated for abnormal findings and any non-physiological changes in endometrial histology were judged by a Central Histopathological Evaluation Committee. Nonphysiological changes in endometrial histology (i.e., benign endometrium, but not observed in the normal menstrual cycle) that were caused by UPA were considered to be progesterone receptor modulator associated endometrial changes (PAEC).

Statistical analysis

A target of 135 patients was set in accordance with the International Conference on Harmonisation E1 guideline for assessing the efficacy and safety of long-term intermittent administration of UPA. Efficacy analyses were conducted on the full analysis set (FAS), defined as all eligible patients treated with UPA and with efficacy data available. No adjustments were made for covariates and missing data were not imputed. Descriptive statistics were used to analyze the efficacy endpoints. The Wilson score method was used to calculate 95% confidence intervals for the rate of amenorrhea (for 35 days and 56 days) and the rate of uterine bleeding normalization. Median time from the end of treatment to return of menstruation was estimated using the Kaplan–Meier method. Mean (*SD*) percent changes from baseline to the end of treatment in fibroid and uterine volume, VAS pain, and UFS-QOL were calculated for each course. Mean (*SD*) changes from the start of each course to the end of each course in hemoglobin concentration were calculated.

Safety analyses were conducted on the safety analysis set (SAS), defined as all eligible patients treated with UPA. Incidences of AEs and drug-related AEs were calculated. Mean (*SD*) endometrial thickness

and hormone concentrations within each course were also calculated.

Results

Demographic and baseline clinical characteristics

Of the 155 patients with uterine fibroids who were enrolled, 140 patients received ≥1 dose of UPA and were included in the FAS and SAS (Figure S2). Of the patients who were included in the analysis, 140, 125, and 111 patients received treatment in Courses 1, 2, and 3, respectively, and 137, 120, and 111 patients completed treatment, respectively. The main reason for patients discontinuing from Course 1 (including the off-treatment period) was because of an AE; from Course 2, it was because patients had exceeded the washout period of 84 days. No patients discontinued from Course 3.

Patients enrolled in the study had a mean age of 42.8 years and had heavy menstrual bleeding (mean PBAC score: 256.7) (Table 1). Most fibroids were intramural and the mean total volume of the three largest fibroids was 123.2 cm^3. Patients reported mild pain (mean VAS score 16.8 mm), the mean UFS-QOL symptom severity score was 40.3, and the mean HRQOL score was 60.6.

Table 1 Baseline characteristics (FAS)

Characteristics	Patients ($N = 140$)
Age (years)	42.8 (5.5)
BMI (kg/m^2)	22.9 (3.5)
Menstrual duration (days)	28.0 (3.1)
PBAC score	256.7 (143.8)
Total volume of three largest fibroids (cm^3)	123.2 (124.6)
Types of fibroids, *n* (%)[a]	
Subserosal	48 (34.3)
Intramural	103 (73.6)
Submucosal	26 (18.6)
Hemoglobin (g/dL)	11.2 (1.8)
VAS pain (mm)	16.8 (22.0)
UFS-QOL	
Symptom severity	40.3 (15.7)
HRQOL	60.6 (19.5)
Endometrial thickness (mm)	8.7 (4.3)
Endocrinology tests	
LH (mIU/mL)	3.8 (2.0)
FSH (mIU/mL)	8.9 (5.9)
Estradiol (pg/mL)	50.3 (47.5)
Progesterone (ng/mL)	0.4 (0.9)

Note: Data are mean (*SD*) unless stated otherwise.
Abbreviations: BMI, body mass index; FAS, full analysis set; FSH, follicle-stimulating hormone; HRQOL, health-related quality of life; LH, luteinizing hormone; PBAC, pictorial blood loss assessment chart; UFS-QOL, Uterine Fibroid Symptom and Health-Related Quality of Life questionnaire; VAS, visual analog scale and [a]Multiple types of uterine fibroids were reported in some patients.

Efficacy outcome measures

Menstrual bleeding

The rates of patients with amenorrhea for 35 days were >90% and similar between all courses (Table 2). At the end of Courses 1, 2, and 3, 92.0%, 96.7%, and 94.6% of patients, respectively, had amenorrhea for 35 days. The rates of amenorrhea for 56 days were 89.1%, 90.8%, and 93.7%, respectively. The median times to amenorrhea after the start of each course ranged from 4.0 to 5.0 days (Table 2). Almost all patients (>99%) achieved uterine bleeding normalization (PBAC <75) for 35 days in all three courses (99.3%, 100%, and 100% for Courses 1, 2, and 3, respectively). The mean PBAC score decreased from baseline by 60% during menstruation in the off-treatment period of Course 1 in patients with amenorrhea and remained decreased for the duration of treatment (Figure S3). Menstruation returned during each off-treatment period within 4 weeks. Median times to the return of menstruation after the end of treatment administration in each course were 25, 26, and 27 days, respectively.

Fibroids and uterine volume

The mean change from baseline to the end of Course 1 in the total volume of the three largest uterine fibroids was −21.5% (Table 2). Total fibroid volume continued to decrease in Courses 2 and 3, with mean changes from baseline of −31.4% and −35.0%, respectively. The mean reduction in fibroid volume at the follow-up visit (Week 24 of Course 3) was −20.7%, which was similar to that observed in Course 1. Mean uterine volume did not change substantially from baseline to the end of Courses 1 and 2 (mean changes were −8.5% and −6.4%, respectively). Although mean uterine volume at the end of Course 3 and the follow-up period increased from baseline by 10.3% and 36.7%, respectively, the SDs were large, suggesting individual differences between patients.

Hemoglobin

Hemoglobin increased from the start of each course to the end of each course, with mean changes of 1.4, 0.9,

Table 2 Efficacy and safety outcomes for patients with uterine fibroids treated with UPA (FAS)

Variable	Course 1 ($N = 137$)	Course 2 ($N = 120$)	Course 3 ($N = 111$)	Follow-up ($N = 111$)
Efficacy outcomes				
Rate of amenorrhea for 35 days, *n* (%)	126 (92.0)	116 (96.7)	105 (94.6)	–
Rate of amenorrhea for 56 days, *n* (%)	122 (89.1)	109 (90.8)	104 (93.7)	–
Rate of patients with uterine bleeding normalization, *n* (%)	136 (99.3)	120 (100.0)	111 (100.0)	–
Time to amenorrhea (days) from start of treatment administration, median (95% CI)	5.0 (−)	4.0 (3.0–5.0)	5.0 (4.0–5.0)	–
Time to recovery of menstruation (days) from end of treatment administration, median (95% CI)[a]	25.0 (24.0–27.0)	26.0 (24.0–29.0)	27.0 (25.0–28.0)	–
Percentage change from BL in total volume of three largest uterine fibroids[b]	−21.5 (36.0)	−31.4 (42.4)	−35.0 (42.2)	−20.7 (49.7)
Percentage change from BL in uterine volume[c]	−8.5 (56.0)	−6.4 (62.0)	10.3 (149.2)	36.7 (167.3)
Change from the start of each course in Hb level (g/dL)[c]	1.4 (1.6)	0.9 (0.7)	0.7 (0.8)	0.2 (0.8)
Change from BL in VAS pain (mm)[c]	−13.2 (22.8)	−12.8 (23.0)	−15.1 (22.6)	−4.8 (27.6)
Change from BL in UFS-QOL score[c]				
Symptom severity	−29.0 (17.5)	−27.2 (18.3)	−25.1 (19.7)	−8.0 (18.4)
Total HRQOL	26.7 (21.3)	24.9 (21.4)	23.3 (19.0)	10.4 (18.9)
Safety outcomes				
Endometrial thickness at end of administration (mm)[d]	7.6 (3.9)	6.9 (3.2)	6.7 (3.4)	7.3 (3.5)
Hormone levels at end of treatment administration[c]				
FSH (mIU/mL)	5.5 (4.2)	5.7 (4.6)	6.3 (4.0)	10.8 (13.4)
LH (mIU/mL)	6.6 (6.1)	6.0 (4.5)	6.6 (6.2)	6.9 (6.8)
Estradiol (pg/mL)	92.0 (105.2)	83.7 (73.4)	88.9 (87.4)	128.5 (126.6)
Progesterone (ng/mL)	0.6 (2.1)	0.7 (2.3)	0.4 (1.5)	3.6 (5.3)

Note: Data are mean (*SD*) unless stated otherwise.
Abbreviations: BL, baseline; CI, confidence interval; FAS, full analysis set; FSH, follicle-stimulating hormone; Hb, hemoglobin; HRQOL, health-related quality of life; LH, luteinizing hormone; QOL, quality of life; SD, standard deviation; UPA, ulipristal acetate; VAS, visual analog scale. [a]Course 1, $N = 126$; Course 2, $N = 116$; Course 3, $N = 105$; [b]Course 1, $N = 136$; Course 2, $N = 118$; Course 3 and follow-up, $N = 110$; [c]Course 1, $N = 136$; Course 2, $N = 119$; Course 3 and follow-up, $N = 111$ and [d]Course 1, $N = 136$; Course 2, $N = 119$; Course 3, $N = 110$; follow-up, $N = 111$.

and 0.7 g/dL in Courses 1, 2, and 3, respectively (Table 2).

Pain and QOL

Substantial reductions in pain (VAS pain) and improvements in QOL (UFS-QOL scores) from baseline were observed in all treatment courses (Table 2), and there were almost no differences in the magnitude of change in VAS pain (Figure S4) and UFS-QOL scores (Figure S5) between courses. Mean VAS pain decreased during treatment in each course and increased to baseline levels during the off-treatment period (Figure S4). Mean changes from baseline to the end of Courses 1, 2, and 3 in VAS pain scores were −13.2, −12.8, and −15.1 mm, respectively. For UFS-QOL scores, symptom severity decreased and HRQOL improved at the end of each treatment course and remained better than baseline levels during off-treatment (Figure S5). Mean changes in UFS-QOL symptom severity scores were −29.0, −27.2, and −25.1, respectively, and mean changes in UFS-QOL HRQOL scores were 26.7, 24.9, and 23.3, respectively.

Safety outcome measures

The incidence of AEs and drug-related AEs during treatment with UPA decreased over time (Table 3). The incidences of AEs in Courses 1, 2, and 3 were 60.0%, 57.6%, and 44.1%, respectively, and most AEs were mild or moderate in severity. The incidences of drug-related AEs were 35.0%, 29.6%, and 16.2%, respectively. Drug-related AEs that occurred in ≥5% of patients during any treatment course were

Table 3 Incidence of AEs and drug-related AEs in patients with uterine fibroids who were treated with UPA, by treatment course (SAS)

Type	Course 1 ($N = 140$)	Course 2 ($N = 125$)	Course 3 ($N = 111$)
AEs, *n* (%)	84 (60.0)	72 (57.6)	49 (44.1)
Severity of AEs, *n* (%)			
Mild[a]	72 (51.4)	58 (46.4)	40 (36.0)
Moderate[b]	26 (18.6)	23 (18.4)	13 (11.7)
Severe[c]	5 (3.6)	2 (1.6)	0 (0.0)
Drug-related AEs, *n* (%)	49 (35.0)	37 (29.6)	18 (16.2)
Drug-related AEs (occurring in ≥5% of patients in any course), *n* (%)			
Metrorrhagia	15 (10.7)	9 (7.2)	8 (7.2)
Genital hemorrhage	8 (5.7)	6 (4.8)	2 (1.8)
Headache	7 (5.0)	3 (2.4)	1 (0.9)
Serious AEs, *n* (%)	3 (2.1)	2 (1.6)	0 (0.0)
Drug-related serious AEs, *n* (%)	2 (1.4)	1 (0.8)	0 (0.0)
Anemia	1 (0.7)	0 (0.0)	0 (0.0)
Embolic cerebral infarction	1 (0.7)	0 (0.0)	0 (0.0)
Pituitary apoplexy	0 (0.0)	1 (0.8)	0 (0.0)

Abbreviations: AE, treatment-emergent adverse events; SAS, safety analysis set; UPA, ulipristal acetate. [a]Could continue in the study without intervention, or no interference with activities of daily living; [b]Could continue in the study with intervention, or interference with activities of daily living and [c]Could not continue in the study (excluding withdrawal due to the subject's request), or prevented engagement in activities of daily living.

metrorrhagia, genital hemorrhage, and headache, with the incidence of each decreasing over time. Across all treatment courses, a total of six serious AEs were reported by five patients and no deaths were reported. Of these, anemia, embolic cerebral infarction, and pituitary apoplexy were considered to be related to UPA; embolic cerebral infarction and pituitary apoplexy were severe and resulted in treatment discontinuation. Other significant AEs that were considered related to UPA included edema peripheral, autoimmune thyroiditis, urticaria, and iron deficiency anemia (one patient each).

Eight hepatic AEs, reported by eight patients, were considered related to UPA. These included hepatic function abnormal (four patients), ALT increased, ALP increased, γ-GT increased, and liver function test (AST and ALT) increased (one patient each). Of these, four cases (two severe, one moderate, one mild) resulted in study discontinuation because the liver function tests for these patients exceeded two times the upper limit of the reference range, which was one of the criteria for study discontinuation.

Mean endometrial thickness gradually decreased over the three courses from 8.7 mm at baseline to 7.6 mm in Course 1, 6.9 mm in Course 2, and 6.7 mm in Course 3 (Table 2). The mean endometrial thickness at the final follow-up visit was 7.3 mm, which was similar to that observed in Course 1 and less than the thickness at baseline. Nonphysiological changes in endometrial histology, as judged by the central committee, occurred in 40.2% of patients at baseline, 52.9% at the end of Course 2, and 43.2% at the end of the follow-up period. There were three cases of endometrial hyperplasia, all of which were nonatypical. No cases of adenocarcinoma or atypical endometrial hyperplasia were detected among patients during the study (Tables 4 and 5).

No safety concerns were detected in the assessments of hormone concentrations or liver function tests. Hormone concentrations remained relatively consistent for the duration of each treatment course (-Figure S6). At Week 12 of each course, mean follicle-stimulating hormone (FSH) concentrations ranged from 5.5 to 6.3 mIU/mL, luteinizing hormone (LH) ranged from 6.0 to 6.6 mIU/mL, estradiol ranged from 83.7 to 92.0 pg/mL, and progesterone ranged from 0.4 to 0.7 ng/mL (Table 2). Mean concentrations of AST and ALT were stable for the duration of the study (Figure S7). Calcium, total protein, albumin, total cholesterol, and low-density lipoprotein cholesterol increased continuously from Week 6 to Week 12 during the on-treatment period in each course and returned to pretreatment levels during the off-treatment/follow-up period. Similarly, hemoglobin A1c, which had increased by Week 12 of the on-treatment period, decreased to pretreatment levels during the off-treatment/follow-up period. There were no notable changes in other laboratory test values including bone turnover markers (data not shown).

Table 4 Summary of consensus diagnoses of endometrial biopsy by the Centralized Histopathological Assessment Committee

Diagnosis by major class	Pretreatment period $N = 140$	Course 2, end of treatment (week 12) $N = 114$ Event (%)	End of study, follow-up period (week 24) $N = 103$
Polyps	0 (0.0)	1 (0.9)	0 (0.0)
Nonatypical hyperplasia	0 (0.0)	2 (1.8)	1 (1.0)
Atypical hyperplasia	0 (0.0)	0 (0.0)	0 (0.0)
Endometrial adenocarcinoma	0 (0.0)	0 (0.0)	0 (0.0)
Other malignant neoplasm	0 (0.0)	0 (0.0)	0 (0.0)
Benign endometrium	140 (100.0)	111 (97.4)	102 (99.0)

Table 5 Detailed endometrial investigations by the Centralized Histopathological Assessment Committee

Major class Subclass	Pretreatment period $N = 420$[a]	Course 2, end of treatment (week 12) $N = 339$[a] Event (%)	End of study, follow-up period (week 24) $N = 309$[a]
Benign endometrium	413 (98.3)	306 (90.3)	103 (34.0)
Proliferative	123 (29.8)	119 (38.9)	94 (31.0)
Secretory	163 (39.5)	45 (14.7)	1 (0.3)
Menstrual	1 (0.2)	0 (0.0)	1 (0.3)
Atrophy	1 (0.2)	5 (1.6)	3 (1.0)
Inactive	0 (0.0)	3 (1.0)	131 (43.2)
Nonphysiological	166 (40.2)	162 (52.9)	7 (2.3)
Other	3 (0.7)	6 (2.0)	103 (34.0)

[a]Total number of assessments.

Discussion

This is the first study to assess the efficacy and safety of three intermittent 12-week courses of 10-mg UPA for treatment of symptomatic uterine fibroids in Asian, specifically Japanese, women. High rates of amenorrhea and uterine bleeding normalization, as well as reductions in fibroid volume and improvement in anemia, were reported during the first course of treatment and were sustained across each of the two additional treatment courses, extending the findings from the 12-week dose-finding study[17] and 12-week randomized trial in Japanese women.[18] In addition, women reported substantial improvements in pain and QOL during treatment, which were maintained for the study duration. Consistent with the clinical trials conducted in Europe,[8,12,13] few safety concerns were reported and UPA was well tolerated, with most AEs being of mild or moderate severity and decreasing in frequency over each of the treatment courses. Together, these findings support the use of 10-mg UPA for long-term management of symptomatic uterine fibroids in Japanese women.

The rates of patients with amenorrhea for 35 days (92%–97%) and uterine bleeding normalization (99%–100%) in this study were similar to the rates for the 10-mg dose in the long-term European PEARL study (35-day amenorrhea: 80%–90%, uterine bleeding normalization: 89%–94%),[13] the 12-week Japanese dose-finding study (35-day amenorrhea: 88%, uterine bleeding normalization: 96%),[17] and the 12-week Japanese randomized trial (35-day amenorrhea: 87%, uterine bleeding normalization: 95%).[18] However, compared with the long-term PEARL study (50%–72% reduction), a lower percentage change in fibroid volume was reported in the current study (20%–35% reduction). Although no formal assessment of fibroid volume and UPA response between European and Japanese women has been conducted, it is possible that racial differences may have contributed to the differences in the reduction in fibroid volume between these studies. The clinical meaningfulness of

the changes in bleeding and fibroid volume was demonstrated by the substantial reductions in UFS-QOL scores that were reported in the current study. Importantly, the changes in mean UFS-QOL scores were maintained for the study duration, and mean scores at the end of each course were within the range for healthy individuals, albeit from a non-Japanese population.[3] Baseline UFS-QOL symptom severity and HRQOL scores were similar to other studies of women with uterine fibroids in Japan,[7,20] which further supports the generalization of the findings to Japanese women with symptomatic uterine fibroids. Although VAS pain scores decreased at each treatment course, the baseline scores were low. The concentrations of progesterone, estradiol, LH, and FSH in the current study were consistent with the concentrations reported for premenopausal women in the midfollicular stage and suggest that ovulation had been suppressed. These findings support the mechanism of action of UPA, which is thought to reduce fibroid volume by acting directly on endometrial tissue and inhibiting ovulation without suppressing ovarian estrogen.[8–10]

Overall, the safety findings in this study were consistent with those reported for European women in the PEARL studies[8,12–14] and with previous 12-week studies in Japanese women.[17,18] The most frequently reported drug-related AEs were metrorrhagia, genital hemorrhage, and headache, all of which decreased in frequency over time. In addition, there were very few serious AEs, including embolic cerebral infarction and pituitary apoplexy. This finding is consistent with those of postmarketing surveillance studies of UPA, which have shown that these AEs occur at very low levels.[20] Also, because UPA did not stimulate the coagulation system or increase the level of pituitary hormones in this study, it is considered unlikely that these AEs would contribute to further complications in clinical settings.

Consistent with studies in European and Japanese women[17,22] and the known mechanism of action of UPA,[23,24] the nonphysiological changes that occurred at the endometrium during treatment with SPRMs were temporary and benign. Mean endometrial thickness was not different from baseline levels by the end of the study. The frequency of nonphysiological endometrial changes at baseline in this study was higher than was reported in the PEARL studies.[8,12–14] Although it is not clear why nonphysiological endometrial changes occurred more frequently in Japanese women, it is possible that racial differences in the hormonal environment may have contributed to this finding.[25]

With the recovery of menstruation, fibroid volume, VAS pain score, and UFS-QOL at the end of the follow-up period returned to the levels reported at the end of Course 1 or baseline. Therefore, these data suggest that repeated 12-week courses of UPA may be required for long-term control of uterine fibroid symptoms. GnRH agonists and antagonists are not recommended for long periods because of the risk of decreased bone mineral density.[7] In this study, UPA did not affect serum estradiol levels or bone turnover markers, thus UPA may be suitable for long-term control of uterine fibroid symptoms. Furthermore, incidences of hot flush were 0.9%–2.4% in each course. In the leuprorelin comparative study in Japanese women, incidences of hot flush were lower in the UPA group than in the leuprorelin group.[18]

In January 2021, the EMA recommended restricting the use of 5-mg UPA because of rare events of severe liver injury that have been reported women who had used 5-mg UPA.[16] In the current study, eight women experienced hepatic treatment-emergent AEs that were considered related to UPA. Of these, two cases were severe and resulted in treatment discontinuation; however, the ALT and AST values of these two cases were less than three times the upper limit of the reference range and did not meet "Hy's law" for hepatotoxicity.[14,26] A key limitation of clinical trials is that the findings may not be generalizable to real-world clinical practice. Although the current study is the first long-term study of UPA in Japanese women, the sample size was insufficient for detecting rare events, a control group was not included, which limits any comparison with GnRH agonists or antagonists, and because the study was open-label, information bias may have affected the subjective assessments. In addition, patients with abnormal hepatic function during the pretreatment observation period were excluded from the study population. Therefore, to minimize any potential risk of liver damage in women treated with UPA, patients with hepatic disorders or abnormal liver function should be excluded from UPA treatment, and, in those who are treated, close monitoring for liver abnormalities should be conducted before treatment commences through to the off-treatment follow-up.

Currently, no long-term drug treatment is available for Japanese women with uterine fibroids who elect to avoid surgery. Long-term administration of

10-mg UPA is effective for reducing symptoms associated with uterine fibroids in Japanese women. Throughout the study, patients experienced improvements in amenorrhea, uterine bleeding normalization, and anemia, as well as sustained improvements in pain and QOL. Treatment with UPA was well tolerated and few safety concerns were reported.

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Authors' Contributions

All authors participated in the interpretation of the study results and in the drafting, critical revision, and approval of the final version of the manuscript. Yutaka Osuga, Yasuaki Nakano, Yuji Yamauchi, and Hitoshi Murakawa were involved in the study design, Yutaka Osuga was an investigator in the study. Yuji Yamauchi conducted the statistical analysis.

Conflict of interest

Yasuaki Nakano, Yuji Yamauchi, and Hitoshi Murakawa are employees of ASKA Pharmaceutical Co., Ltd. Yutaka Osuga has received honoraria from Mochida Pharmaceutical Co., Ltd., Otsuka Pharmaceutical Co., Ltd., Fuji Pharma Co., Ltd., Bayer Ltd, ASKA Pharmaceutical Co., Ltd., Nippon Shinyaku Co., Ltd., and Nobelpharma Co., Ltd.

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Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Figure S1 Study design and schedule.
Abbreviations: AE, adverse event; UFS-QOL, Uterine Fibroid System Quality of Life questionnaire; VAS, visual analog scale.
[†]Ulipristal acetate (UPA) was initiated within the first 7 days of menstruation in Course 1. For Courses 2 and 3, UPA was initiated within 7 days of the start of the next menstruation period at the end of each treatment period.

Figure S2. Patient disposition.
Abbreviation: AE, adverse event.

Figure S3. Mean percentage change in pictorial blood loss assessment chart (PBAC) score during menstruation in nonamenorrheic patients over the three ulipristal acetate (UPA) treatment courses. Amenorrhea was defined as PBAC score ≤ 2. Treatment with UPA started at Week (Wk) 1 and ended at Wk 12. Error bars indicate standard deviation.
Abbreviation: ME, end of menstruation.
[†]Before administration of the first dose of UPA.

Figure S4. Mean change from baseline in visual analog scale (VAS) pain over the three ulipristal acetate (UPA) treatment courses. Treatment with UPA started at Week (Wk) 1 and ended at Wk 12. Error bars indicate standard deviation.
[†]Before administration of the first dose of UPA.

Figure S5. Mean change from baseline in (a) Uterine Fibroid Symptom and Health-Related Quality of Life questionnaire (UFS-QOL) symptom severity scores and (b) UFS-QOL health-related quality of life (HRQOL) scores over the three ulipristal acetate (UPA) treatment courses. Treatment with UPA started at Week (Wk) 1 and ended at Wk 12. Error bars indicate standard deviation.
[†]Before administration of the first dose of UPA.

Figure S6. Mean (a) estradiol level, (b) progesterone level, (c) luteinizing hormone (LH) level, (d) follicle-stimulating hormone (FSH) level over the three ulipristal acetate (UPA) treatment courses. Treatment with UPA started at Week (Wk) 1 and ended at Wk 12. Error bars indicate standard deviation.
Abbreviation: ME, end of menstruation.
[†]Before administration of the first dose of UPA.

Figure S7. Mean (a) aspartate aminotransferase (AST) and (b) alanine aminotransferase (ALT) over the three ulipristal acetate (UPA) treatment courses. Treatment with UPA started at Week (Wk) 1 and ended at Wk 12. Error bars indicate standard deviation.
Abbreviation: ME, end of menstruation.
[†]Before administration of the first dose of UPA.

