Long-term medical management of uterine fibroids with ulipristal acetate

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Objective: To investigate the efficacy and safety of repeated 12-week courses of 5 or 10 mg daily ulipristal acetate for intermittent treatment of symptomatic uterine fibroids.
Design: Double-blind, randomized administration of four 12-week courses of ulipristal acetate.
Setting: Gynecology centers.
Patient(s): Four hundred fifty-one subjects with symptomatic uterine fibroid(s) and heavy menstrual bleeding.
Intervention(s): Four repeated 12-week treatment courses of daily 5 or 10 mg ulipristal acetate.
Main Outcome Measure(s): Endometrial safety and general safety, laboratory parameters, amenorrhea, controlled bleeding, fibroid volume, quality of life (QoL), and pain.
Result(s): Efficacy results, such as bleeding control and fibroid volume reduction, were in line with previously published data. Pain and QoL showed marked improvements from screening, even during the off-treatment intervals. The safety profile of ulipristal acetate was confirmed, and repeated treatment courses did not increase the occurrence of adverse reactions. There were no significant changes in laboratory parameters during the study. The percentage of subjects with endometrial thickness $\geq$16 mm was 7.4% (all subjects) after the first treatment course and returned to below screening levels (4.9%) in subsequent treatment courses. As in previous studies, ulipristal acetate did not increase the occurrence of endometrial features of concern. The frequency of nonphysiological changes did not increase with repeated treatment. They were

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observed in 17.8% and 13.3% of biopsies after treatment courses 2 and 4, respectively, and were reversible after treatment cessation.
Conclusion(s): The results of this study demonstrate the efficacy and further support the safety profile of repeated intermittent treatment of symptomatic fibroids with ulipristal acetate.
Clinical Trial Registration Number: NCT01629563. (Fertil Steril® 2016;105:165–73.
Key Words: Ulipristal acetate, uterine fibroid, pain, bleeding, fibroid volume, long-term treatment

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

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

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

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

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

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

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

MATERIALS AND METHODS

Study Design and Oversight

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

Study Population

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