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

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

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J.D. has been a member of the Scientific Advisory Board (SAB) of PregLem S.A. since 2007. He held PregLem stocks related to SAB activities that he sold in October 2010 at PregLem's full acquisition by the Gedeon Richter Group. There is no relationship between stock payment value and future commercial performance of the study drug. R.H. and his institution received a grant for this study, study equipment and support for travel to the investigator meetings for **P**GL4001 (ulipristal acetate) **E**fficacy **A**ssessment in **R**eduction of symptoms due to uterine **L**eiomyomata (PEARL IV). O.D. and his institution received a grant for this study and support for travel to the investigator meetings. D.M. and her institution received a grant for this study. H.-J.A. and his institution received a grant for this study, study equipment and support for travel to the investigator meetings for PEARL IV. J.Z. and his institution received a grant for this study, study equipment and support for travel to the investigator meetings for PEARL IV. Z.K. and her institution received a grant for this study and support for travel to the investigator meetings for PEARL IV. M.C.D. and his institution received a grant for this study and support for travel to the investigator meetings for PEARL IV. H.F. and his institution received a grant for this study. D.H.B. has been a member of the Scientific Advisory Board (SAB) of PregLem S.A. since 2007. He held PregLem stocks related to SAB activities that he sold in October 2010 at PregLem's full acquisition by the Gedeon Richter Group. There is no relationship between stock payment value and future commercial performance of the study drug. P.B. is a member of PregLem's SAB. He held PregLem stocks related to SAB activities that he sold in October 2010 at PregLem's full acquisition by the Gedeon Richter Group. There is no relationship between stock payment value and future commercial performance of the study drug. B.C.J.M.F. is a member of PregLem's SAB. He held PregLem stocks related to SAB activities that he sold in October 2010 at PregLem's full acquisition by the Gedeon Richter Group. There is no relationship between stock payment value and future commercial performance of the study drug. E.B. is an employee of PregLem S.A. She held PregLem stocks related to her employment that she sold in October 2010 at PregLem's full acquisition by the Gedeon Richter Group. There is no relationship between stock payment value and future commercial performance of the study drug. P.T. and his company CROS NT received payment for consultancy and support for travel to meetings. I.O. and his company Ostermed received payment for consultancy and support for travel to meetings. E.L. is a member of PregLem's SAB. He received payment for consultancy and held PregLem stocks that he sold in October 2010 at PregLem's full acquisition by the Gedeon Richter Group. There is no relationship between stock payment value and future commercial performance of the study drug.
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**Conclusion(s):** Repeated 12-week courses of daily oral ulipristal acetate (5 and 10 mg) effectively control bleeding and pain, reduce fibroid volume, and restore QoL in patients with symptomatic fibroids.
**Clinical Trial Registration Number:** NCT01629563 (PEARL IV). (Fertil Steril® 2015;103: 519–27. ©2015 by American Society for Reproductive Medicine.)
**Key Words:** Repeated intermittent use, ulipristal acetate, uterine fibroid, quality of life, long-term treatment

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

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

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

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

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

## MATERIALS AND METHODS

### Study Design and Oversight

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

### Study Population

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

### Randomization and Intervention

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