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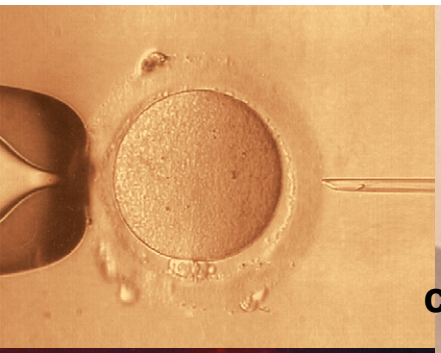

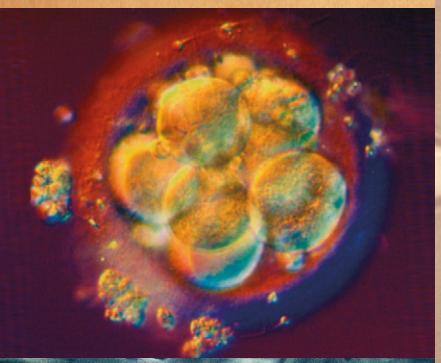

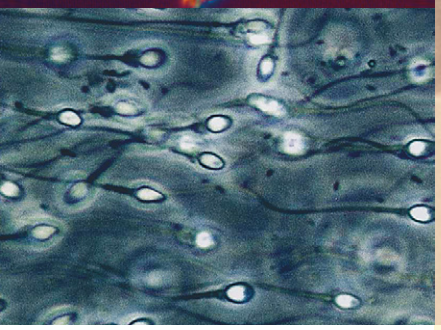

Intermittent Treatment with Ulipristal Acetate for Conservative Treatment of Uterine Leiomyoma and Bleeding control in Patients with Hypermenorrhoea caused by Uterine Leiomyoma (Joint statement of the DGGEF e. V. and the BVF e. V.)

Rabe T, Ahrendt HJ, Albring C, Bitzer J, Bohlmann MK
Egarter C, König K, Mueck AO, Peters K, Römer T
Sänger N, Tinneberg HR, Wallwiener M

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Intermittent Treatment with Ulipristal Acetate for Conservative Treatment of Uterine Leiomyoma and Bleeding control in Patients with Hypermenorrhoea caused by Uterine Leiomyoma*

Joint statement of the German Society of Gynaecological Endocrinology and Reproductive Medicine (DGGEF e.V.) and the Professional Association of Gynaecologists (BVF) e.V.

T. Rabe[1] (lead author) in cooperation with the working group "Conservative treatment of uterine leiomyoma and hypermenorrhoea" (in alphabetical order): H.-J. Ahrendt[2], C. Albring[3], J. Bitzer[4], M. Bohlmann[5], C. Egarter[6], K. König[7], A. O. Mueck[8], K. Peters[9], T. Römer[10], N. Sänger[11], H. R. Tinneberg[12], M. Wallwiener[1]

Approximately 24 million women in Europe and more than 20 million women in North America mainly between the ages of 35 and 55 years suffer from uterine myomas; this is 40% of all women in this age group. Myoma-derived symptoms manifest themselves by strong uterine bleeding, anaemia, pain and infertility. Thereby, the quality of life of many women is impaired to a high extent and in many cases this ultimately leads to hysterectomy.

Two randomised double-blind studies published in 2012 demonstrated the efficacy of the progesterone receptor modulator ulipristal acetate in the treatment of uterine myomas in women who were eligible for surgery in order to control their hypermenorrhoea. Considerable side effects did not occur over the course of 3 months with dosages of 5 as well as 10 mg of UPA. A reduction of the uterine bleeding was already observed after 7 days, along with a volume reduction by 40% in the uterine myomas within 3 months, which also appeared to be sustained for 6 months after the end of treatment. Esmya®, a tablet with 5 mg ulipristal acetate, was approved by the EMA for the preoperative treatment of symptomatic leiomyoma in spring 2012.

The PEARL-III study examined the control of bleeding, volume reduction in myoma, quality of life and pain in symptomatic myoma patients after four 3-month courses of UPA treatment cycles (10 mg/day). Each 3-month treatment cycle was followed by 10 days of double-blind treatment with either 10 mg norethisterone acetate (NETA) or Placebo and a treatment-free period of two menstrual cycles. The follow-up period was three months after the end of the fourth treatment course. The NETA therapy had no effect on the primary and main secondary study parameters. During the study, a control of the bleeding could be achieved in 94% of the patients, and 90% were seen to develop amenorrhea. The total volume reduction (median) of the three largest myomas after 4 treatment cycles was about 72% and 82% of the patients demonstrated a reduction in volume of ≥ 25%. In 95% of the patients, an operation was no longer necessary during the entire study period. Drug-safety examinations did not reveal any particular risks and the profile of side-effects showed no differences to those found in the PEARL-I and PEARL-II studies. The good tolerance profile of UPA was maintained over repeated treatment courses.

In the PEARL-III study, women also reported on essential improvements in the quality of life including a reduction of pain, fear and depression during the treatment. The UFS QOL scores at the beginning of the study were slightly less severe than in some former studies. At the end of the UPA treatment cycles, the severity of the symptoms and the quality of life scores were comparable with those seen in follow-ups for patients who had been subjected to a hysterectomy, myomectomy, embolisation of the uterus or following a focused high-intensity ultrasonography (not recommended in infertility patients)..

Since January 2014, there has been a change in the authorization for a further 3-month cycle of therapy in symptomatic patients with uterine myomas, who are eligible for surgery.

In May 2015, UPA has been approved for the long-term intermittent therapy of symptomatic patients with uterine fibroids. UPA now has two indications.
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Key words: uterus myomatosus, hypermenorrhoea, anaemia, progesterone receptor modulator, ulipristal acetate, amenorrhea

Introduction

Uterine leiomyomas (fibroids) are benign, hormone-sensitive tumors of the smooth muscles, occurring in 20–40% of women of childbearing age [1, 2]. Fibroids are thus the most common benign uterine tumors for women of reproductive age. The most frequent concomitant symptoms are menorrhagia and iron deficiency anaemia, which sometimes cannot be adequately treated with iron substitution alone [3–5]. Heavy menstrual bleeding increases the number of consultations of a physician and results in an increased absence from work [5]. Other symptoms include abdominal pain, dysmenorrhoea, pressure effects, pollakiuria, nycturia and constipation, as well as a negative effect on fertility, depending on the location and size of the fibroids. The quality of life is significantly impaired [6–9].

Therapeutic Options

Treatment strategies mainly consist of surgical and radiological procedures; the options of medical treatment were limited (Tab. 1) [3, 9–13].

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From: University Women's Hospital Heidelberg; [2]Gynaecology Practice, Clinical Research and Further Training, Magdeburg; [3]Berufsverband der Frauenärzte e. V. Hannover; [4]Basel, CH; [5]University Hospital Mannheim; [6]Dept. of Gyn. Endocrinology and Reproductive Medicine, Medical University of Vienna, A; [7]Berufsverband der Frauenärzte e.V., Steinbach/Ts; [8]Centre for Women's Health, University Hospital Tübingen; [9]Hamburg; [10]Evangelical Hospital, Köln-Weyertal gGmbH, Cologne; [11]Clinic for Gynaecology and Obstetrics, Frankfurt/M.; [12]University Women's Hospital, Gießen and Marburg University Hospital GmbH, Gießen

Correspondence: Prof. Dr med. Dr h.c. mult. Thomas Rabe, Department of Gynaecological Endocrinology and Reproductive Medicine, Universitäts-Frauenklinik Heidelberg, D-69120 Heidelberg, Im Neuenheimer Feld 440; e-mail: thomas_rabe@yahoo.de

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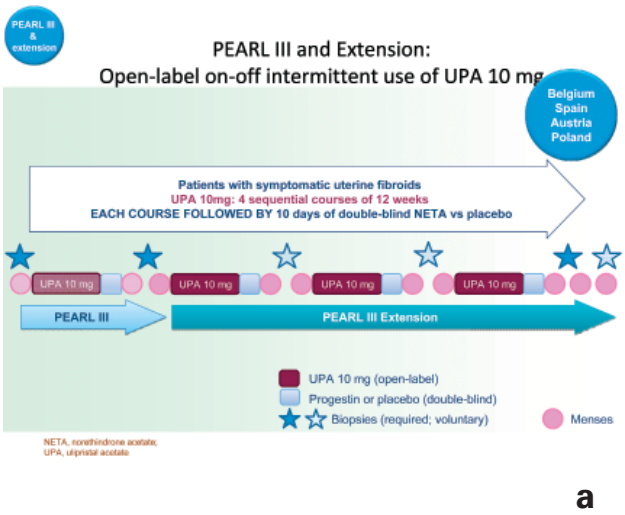
Table 1. Different therapeutic options for uterine leiomyomas. © Thomas Rabe

Therapy approach	Suitable patient group	Advantages	Disadvantages	Possible consequences for fertility and subsequent pregnancies
Ulipristal acetate (5 mg/day)	Myoma patients with moderate to severe symptoms for treatment in women (young, desire to preserve fertility or uterus, premenopausal, presurgical)	– Non-surgical long-term treatment – Therapy is no longer limited in number of repeated treatment cycles of 3 months. Studies on interval therapy have been conducted.	None	First case reports are described here; further data are being prepared
GnRH agonists (gonadotropin-releasing hormone)	Presurgical treatment in young or premenopausal women	Non-surgical	– Time-limited treatment with myoma regrowth after discontinuation – Adverse reactions – Difficult subsequent surgery due to fibrosis of the myoma to the myometrium	None
GnRH agonists (gonadotropin-releasing hormone) + estrogen/gestagen administration ("add back")	Presurgical treatment in young or premenopausal women	Non-surgical	– Time-limited treatment with myoma regrowth after discontinuation – Difficult subsequent surgery due to fibrosis of the myoma to the myometrium	None
GnRH antagonists	Presurgical treatment in young or premenopausal women	Non-surgical	– Time-limited treatment with myoma regrowth after discontinuation	No data
Gestagen therapy	Administration for women with myomas for bleeding control	Non-surgical	– Missing long-term data – Adverse reactions – No proof of efficacy for myoma therapy	No data
Hysterectomy	Women, who require a hysterectomy, approach menopause soon or do not wish to preserve their fertility	Irrevocable therapy	– Loss of fertility, surgical morbidity and/or mortality – Cost-intensive – Only method that definitively removes the myoma	Complete loss of fertility
Myomectomy	– Women with visible and/or palpable myomas without size limitation – Removal of smaller myomas also possible endoscopically on an outpatient basis	Fertility preservation	– Recurrent myomas possible – Surgical morbidity – Risk of uterine rupture, for all myomas – Posterior wall myomas more frequent than with anterior wall myomas – Adhesion formation	– Risk of uterine rupture during subsequent pregnancy – Adhesion formation can impair fertility
Myolysis/cryomyolysis	Women without desire to preserve fertility with several, small myomas	Uterus preservation, outpatient treatment method	– Risk of adhesions – Less effective with large and multiple myomas, under – or overtherapy – Subsequent pregnancies are not recommended	– Lower fertility due to adhesion formation – Risk of uterine rupture during the pregnancy – Pathological placenta development
UAE ("uterine artery embolization")	Women with small myomas (< 8 cm), without sub-serous, sub-mucous location or pedunculated	The entire uterus is treated, no blood loss and no surgical procedure with opening of the abdominal cavity	– Pain – Possible post-embolization syndrome – Possible severe complications – Effects on fertility still have to be examined – Cost-intensive – Frequent rate of second surgeries – Conduction only through specialized radiologists – Long-term effects of myoma necrosis not known	– Risk of premature ovarian insufficiency – Necrosis formation – Pathological placenta development – Risk of uterine rupture with subsequent pregnancy
LUAO ("laparoscopic uterine artery occlusion")	Women with sub-serous myomas	Effective with adequate experience with the method	– Experience with the method required – Depending on the location of the myomas – Fertility unclear – Insufficient long-term data – Long-term effects of myoma necrosis not known	– No data – Risk of uterine rupture with subsequent pregnancy
MRgFUS ("magnetic resonance imaging-guided focused ultrasound surgery") respectively HIFU ("high-intensity focused ultrasound")	Women with small myomas (> 3 – < 10 cm)	– Without intra-abdominal surgical procedure – No blood loss – Patient quickly fit again	– Fertility unclear – Recurrence rate unclear – Cost-intensive – Insufficient long-term data – Conduction only through specialized radiologists – Long-term effects of myoma necrosis not known	– Currently no sufficient data yet – Risk of uterine rupture with subsequent pregnancy
Oral hormonal contraceptives	Patients with smaller myomas and bleeding disturbances	– Non-surgical – Contraception: good, also preventative effect in case of light to moderate bleeding disturbances	– Breakthrough bleeding possible, especially due to submucous myomas – Influence on myoma growth questionable	None



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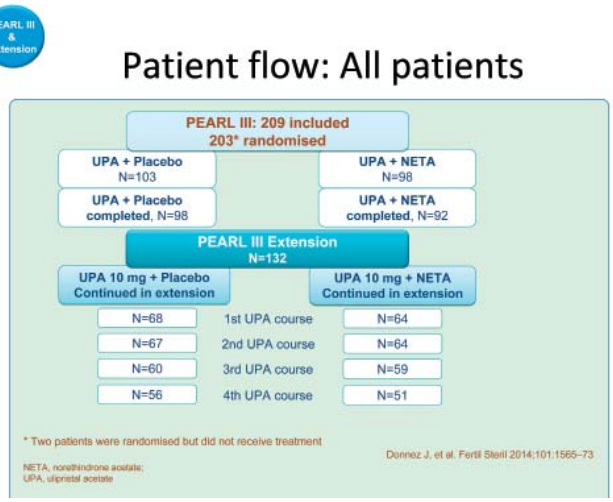

b

PEARL III & Extension

BASELINE CHARACTERISTICS

Characteristic (ITT Population)		Open-label (UPA 10 mg/day)	Double-blind population	
Study population (N)		Total (132)	Placebo (68)	NETA (64)
Mean age, years (range)		40.5 (20–48)	40.5 (23–48)	40.6 (20–48)
Ethnic origin:	White	121 (91.7%)	63 (92.6%)	58 (90.6%)
	Black	8 (6.1%)	3 (4.4%)	5 (7.8%)
	Asian	1 (0.8%)	1 (1.5%)	0
	Hispanic	2 (1.5%)	1 (1.5%)	1 (1.6%)
	Other	0	0	0
Mean weight, kg (range)		68.73 (41–110)	69.40 (48.5–110)	68.01 (41–98.7)
Mean body mass index, kg/m² (range)		25.39 (18–39.8)	25.27 (18.4–39)	25.52 (18–39)

NETA, norethindrone acetate
UPA, ulipristal acetate

c

Figure 1. (a). PEARL-III study: This study concerns the question of whether 10 mg UPA over 3 months, followed by a 10-day administration of 10 mg NETA in a double-blind study improved endometrial stability and cancels out the possible PAEC changes to the endometrium. This treatment was then repeated a total of 3x in the PEARL-III extension study with the second menstrual period after the end of the first UPA treatment, with the aim of researching the clinical efficacy and safety of an intermittent long-term therapy with 10 mg ulipristal acetate (UPA) per day for 3 months each for the treatment of symptomatic uterine fibroids, and to assess the clinical benefit of a 10-day NETA administration regarding the reversibility of any anti-progesterone effect of ulipristal acetate on the endometrium and regarding the influence on menstrual bleeding after the end of therapy. **(b)**. PEARL-III study: Baseline characteristics of the patients for the sequential treatment with 10 mg UPA over 3 months with subsequent therapy with NETA (10 mg/day) or placebo over a total of 4 treatment cycles. Of the total 25 women who discontinued the study, a possible 6 desiring surgery have only responded badly to UPA therapy ("non-responder"). However, this should not have any influence on the study results. **(c)**. PEARL-III extension study: Baseline characteristics of the patients. Mod. according to: J. Donnez, et al. Long-term treatment of uterine fibroids with ulipristal acetate. Fertil Steril 2014; 101: 1565–73 as well as from internal documents ("courtesy of GR/PregLem SA"). Reprint with approval of Gedeon Richter AG.

PEARL-I, -II, -III, and -IV studies

In 2012, Donnez et al. [14, 15] presented the results of the PEARL-I and -II-studies.

Study Description

The study design for the PEARL-I, -II and -III studies and the most important study results are displayed in Table 2; Figure 1 shows those from the PEARL-III studies.

Study Design

PEARL-III study

- European open-label, long-term interval therapy with 10 mg UPA, for 12 weeks in 209 patients with symptomatic uterine leiomyoma including severe hypermenorrhoea.
- Directly after administration of ulipristal acetate (UPA) randomised, double-blind administration of norethisterone acetate (10 mg/day) for 10 days vs. placebo.

PEARL-III extension study

The optional extension to undergo 3 further cycles of 12 weeks with 10 mg UPA daily, each followed by the double-blind norethisterone acetate/placebo administration was followed by 132 patients.

Study Objective

The objective of this multicentric clinical phase III study was:

- to investigate the clinical efficacy and safety of intermittent long-term therapy with 10 mg ulipristal acetate per day for 3 months each for treatment of symptomatic uterine fibroids, and
- to assess the clinical benefit of a 10-day NETA administration regarding the reversibility of an anti-progesterone effect of ulipristal acetate on the endometrium and regarding the influence on menstrual bleeding after the end of therapy.
- Endometrium histology

Results of the PEARL-III study

The PEARL-III study investigated bleeding control and reduction of fibroid volume.

Bleeding Control (Fig. 2a)

- High amenorrhoea rate: 79% of patients had amenorrhoea after the first treatment cycle and 88–90% after repeated administration.
- Start of amenorrhoea within 10 days of 10 mg UPA, whereby mean (median) time to amenorrhea was 9.4 days (4.0 days) for the first treatment course and 4.2 days (3 days) for the fourth treatment course.
- Effective bleeding control: In 94% of patients, bleeding could be controlled

Table 2. PEARL-I, -II , -III and -IV studies. © Thomas Rabe

Study	Study design	Results
PEARL-I	**Study design:** Randomized comparative study for evaluation of treatment with 5 or 10 mg ulipristal acetate (UPA) in comparison to placebo administered for 12 weeks in patients with uterine fibroids, who are eligible for surgery. **Primary study goals:** Investigating the efficacy and safety of orally administered UPA in comparison to placebo for treatment of symptomatic uterine fibroids in patients, who were eligible for surgery. **Primary efficacy endpoint:** Percentage of patients with bleeding control in week 13. **Efficacy endpoints:** – Reduction of the myoma volume in week 13, evaluated by centralised magnetic resonance imaging (MRI) – Bleeding pattern (28 days PBAC) – Rate of amenorrhea (PBAC ≤ 2 in week 9 and 13) – Reduction of the uterine and myoma volume (percentage of the women with at least 25% reduction) – Change of the haemoglobin, haematocrit and ferritin value – Pain – Quality of life **Study centres:** Europe and India	The bleeding control and the reduction of the myoma volume were examined during the study. **Bleeding control:** Symptomatic patients with hypermenorrhea experienced a control of the hypermenorrhea with 91% of the women on 5 mg ulipristal acetate, with 92% of the women on 10 mg UPA and with 19 % of the women on placebo ($p < 0.001$ for the comparison of each UPA dose with placebo) at end of treatment. The amenorrhea rates were at 73%, 82%, and 6% (for 5 mg UPA, 10 mg UPA and placebo), respectively, with amenorrhea occurring within 10 days in most patients receiving UPA. **Total myoma volume (centralised MRI examination):** The changes of the total volume of the myomas (medians) were –21%, –12%, and +3% ($p = 0.002$ for the comparison of 5 mg UPA with placebo and $p = 0.006$ for the comparison of 10 mg UPA with placebo). **Conclusions:** The treatment with UPA over a period of 3 month led to effective control of excessive bleeding caused by uterine fibroids and at the same time it decreased the myoma size.
PEARL-II	**Study design:** Randomized comparative study for evaluation of the treatment with 5 or 10 mg UPA in comparison to leuprorelin acetate administered for 12 weeks in patients with uterine fibroids, who are eligible for surgery. **Primary study goals:** Proof of efficacy (non-inferiority) of UPA vs. GnRHa for reduction of increased uterine bleeding before a surgery; proof of efficacy (superior) regarding safety and tolerability concerning hot flushes and estrogen level. **Primary efficacy endpoint:** Percentage of patients with bleeding control in week 13. **Efficacy endpoints:** – Bleeding pattern (28 days PBAC) – Amenorrhea rate (PBAC ≤ 2 in week 9 and 13) – Changes compared to base line regarding myoma and uterine volume (based on ultrasound examinations) – Reduction of the uterine and myoma volume (percentage of the women with at least 25 % reduction) – Change of the haemoglobin, haematocrit and ferritin value – Pain – Uterine fibroid symptom and quality of life questionnaire **Study centres:** Europe and Israel	The bleeding control and the reduction of the myoma volume were examined during the study. **Bleeding control:** Both the daily 5 mg and the daily 10 mg dose of UPA were not inferior regarding the uterine bleeding control and caused hot flushes significantly less frequent compared to the 1× monthly administration of leuprorelin acetate. The response rates to the treatment were good in all 3 study groups, PBAC scores below 75 (primary efficacy endpoint) could be observed at end of treatment in 90% of the patients on 5 mg UPA, in 98% on 10 mg UPA and in 89% on leuprorelin acetate. Median times to amenorrhea were 7 days for patients receiving 5 mg of UPA, 5 days for those receiving 10 mg of UPA, and 21 days for those receiving leuprorelin acetate. **Myoma volume (of the 3 largest myomas; ultrasound measurement):** All 3 therapy forms led to a reduction of the uterine volume, even though the decrease in the leuprorelin acetate group was more pronounced than in the UPA groups. A reduction of the total volume of the 3 largest myomas could be recorded in all 3 groups without significant group differences. At exploratory analyses across the subpopulation of patients that did not undergo a surgery, the myomas started to enlarge approx. 1 month after the last dose of leuprorelin acetate . The reduction of the myoma volume however seemed to be sustained in the majority of the patients on UPA for the next 6 months after the end of therapy. These findings can possibly be explained by the apoptosis of leiomyoma cells. **Side effects:** Patients In the UPA group suffered significantly less from estrogen deficiency symptoms such as hot flashes. **Safety:** Estrogen levels remained at midfollicular levels under UPA and hot flushes occurred significantly less frequently than with leuprorelide acetate. **Conclusions:** The treatment with UPA over a period of 3 months led to comparable bleeding control as leuprorelin acetate and decreased the myoma size. In the UPA-group the decrease of myoma size after stopping the active treatment remained stable, whereas in the leuprorelide acetate the myoma increased in size again. The safety profile of UPA is improved compared to leuprorelide acetate.
PEARL-III	**Study design:** Open-label phase III study in symptomatic myoma patients with 4 UPA (10 mg/day) treatment cycles of 3 months each, followed by 10 days of 10 mg NETA (norethisterone acetate) or placebo and a treatment break of 2 menstruation cycles each as well as a follow-up examination **Primary efficacy endpoint:** Percentage of the patients in amenorrhea at the end of each UPA treatment cycle **Primary study goals:** Investigating the clinical efficacy and safety of the long-term intermittent 3-month administration of ulipristal acetate 10 mg per day for the treatment of symptomatic uterine myoma and assessing the clinical benefit of a 10-day administration of NETA to reverse the anti-progesterone effect of ulipristal acetate on the endometrium and its effect on post-treatment menstrual bleeding. **Secondary efficacy endpoint:** Reduction of myoma volume (measured by ultrasound); pain, quality of life; **Study centres:** Europe	Bleeding control, reduction of the myoma volume, impact on the quality of life, drug safety and a possible effect of a subsequent dose of 10 mg norethisterone acetate (NETA) were examined in the study. Bleeding control: Bleeding control could be observed in 94 % of patients, and 90% achieved amenorrhea. **Myoma volume:** The median volume reduction of the three largest myomas was 72% after 4 treatment cycles. 82% of the patients demonstrated a clinically significant reduction in volume of ≥ 25%. **Quality of life:** 95% of the patients did not undergo surgery. Drug safety: Good tolerance even after repeated treatment courses. No clinically relevant adverse events. Norethisterone acetate (10 mg/day) over the course of 10 days at the end of each therapy cycle had no positive/negative effect on the shrinking of the myomas and the bleeding control under treatment. Since January 28, 2014 there has been an amendment to the approval for a further treatment cycle in symptomatic patients with uterine fibroids, who are eligible for surgery.

▶

Table 2 (continuation)

Study	Study design	Results
PEARL-IV	**Study design:** Randomized comparative phase III study for evaluation of the treatment with 5 or 10 mg UPA in symptomatic myoma patients with 4 UPA treatment cycles of 3 months each and a treatment break of 2 menstruation cycles between treatment courses as well as a follow-up examination **Primary efficacy endpoint:** Percentage of the patients in amenorrhea at the end of all UPA treatment cycles **Primary study goals:** Investigating the clinical efficacy and safety of the long-term intermittent 3-month administration of ulipristal acetate 5 mg or 10 mg per day for the treatment of symptomatic uterine myoma **Secondary efficacy endpoint:** Reduction of myoma volume (measured by ultrasound); pain, quality of life; **Study centres:** Europe	Bleeding control, reduction of the myoma volume, impact on the quality of life and pain and drug safety were examined in the study. **Full study results not published yet. According to Press release** the study could demonstrate that 70% of the patients on the 5 mg dose were in amenorrhea after the fourth treatment course. In addition, fibroid volume reduction from baseline was on average 72% and uterine volume decreased significantly during the study and quality of life and pain were improved in comparison to baseline, even during the off treatment intervals

(amenorrhoea or only spotting at the end of each therapy cycle).
– Positive effect of repeated administration: The strength of bleeding during the therapy-free period continued to decrease after each UPA treatment cycle.

Fibroid volume and volume-linked symptoms (Fig. 2b)

– Clinically significant reduction of the 3 largest fibroids: After 4 treatment cycles, 70% of patients showed a volume reduction of the 3 largest fibroids of more than 50%.
– Of the 209 patients who took part in PEARL-III, volume reduction of the 3 largest fibroids was 45.1% after 3 months of treatment (n = 194). Of the 132 patients who took part in the PEARL-III extension study, volume reduction of the 3 largest fibroids was 49.9% after 3 month (n = 130) and increased to 72.1% after 4 times 3 months (n = 96).
– Permanent effect: Follow-up observation continued for only 3 months, in contrast to earlier studies. During this period, there were no signs of a rebound effect.
– Less pain: The distinct reduction in pain during the first treatment cycle was maintained with repeated administration.
– Symptoms such as incontinence and dyspareunia correlate with the fibroid volume [16]. The size, number and localization of the fibroids certainly play a role here.

Symptom: Impaired quality of life

The quality of life was assessed at several points during the studies using 3 specific scoring systems. The validated Uterine Fibroid Symptom and Quality of Life (UFS-QoL) questionnaire contains 2 scoring systems, the symptom severity with bleeding, lower abdominal pain, frequency of urination and fatigue and the general health-related questionnaire for quality of life (HRQL) containing sections on anxiety, activity, energy/mood, self-determination, self-confidence and sexual activity. The recognised EQ-5D questionnaire also includes quality of life related to routine activities such as mobility, self-care, usual activities, but also pain/discomfort and anxiety/depression, all with a three-level scale.

It is well-known that fibroids impair the quality of life [17]. In the PEARL-III study, all 3 scoring systems showed clearly a reduced quality of life before the start of therapy. Quality of life normalised under therapy in the PEARL-III study and the level of healthy women was reached (UFS-QoL). A reduction in anxiety and depression could also be documented (EQ-5D).

It could have been expected that the fibroid-related symptoms would at least partly return between treatment intervals. However, the strength of menstrual bleeding continued to decrease after each treatment cycle. It was also demonstrated 3 months after the last treatment cycle that reduction in fibroid volume and the improvements in pain and quality were largely maintained.

Endometrial Changes

In the PEARL-I study, the median endometrial thickness was not significantly different between the groups. For a small portion of patients who received ulipristal acetate, the endometrial thickness was >16 mm at end of the 3-month treatment course; in all cases, this regressed during follow-up. At the end of the treatment, the centrally appraised biopsy samples exhibited no malignant or premalignant lesions or hyperplasia; only in one case in PEARL-II a hyperplasia was observed; benign non-physiological endometrial changes were observed more frequently in the 5 mg and 10 mg ulipristal acetate group than in the placebo group (62%, 57%, and 6%, respectively) in PEARL-I. Up to week 38 (6 months after the end of the treatment), these changes were no longer detectable; in the placebo group, there was one case of a complex atypical hyperplasia, which is not unusual in relation to the sample size and selection of patients (age group, fibroids and hypermenorrhoea).

Barlow et al [18] analysed the bleeding pattern in the PEARL-I study in more detail and found that, in patients with longer, frequent or irregular bleeding, the incidence of submucosal fibroids was increased (UPA 5 mg 100% and UPA 10 mg 78.6%). However, there was no correlation with progesterone receptor modulator associated endometrial changes (PAEC).

In the PEARL-III study, the endometrial thickness was grouped into the following classes: up to 4 mm; 4–16 mm and > 16 mm.

a) In total, the endometrial thickness decreases with additional treatment cycles.
b) The frequency of endometrial thickening (> 16 mm) was < 10% in all treatment cycles.

c) For the occurrence of PAEC (PRM-associated endometrial changes), no cumulative effect could be observed with repeated administration.

The typical changes of the endometrium (PAEC), which were confirmed by at least 2 independent pathologists, were observed in 18/171 (11%), 45/176 (26%), and 22/87 (25%) of biopsied patients at study enrolment and 6 weeks after the first and fourth treatment cycle, respectively. During the 3-month follow-up period, it was confirmed that PAEC is rapidly reversible. No endometrial hyperplasia was observed.

Drug Safety Data

In both of the first clinical studies (PEARL-I and -II), no considerable clinical side effects were observed: hot flushes (12.7%), reversible endometrium thickening (10–15%), headache (6.4%) and breast tenderness in a few cases. In comparison to treatment with the GnRH analogue, leuprorelin, significantly fewer side effects occurred with UPA.

In the PEARL-III study, no essentially different pattern of side effects was found; no negative effect on the clinical chemistry parameters or on the thyroid and adrenal glands was observed. The frequency of side effects did not increase with repeated administration in the PEARL-III study.

Final Evaluation

Fibroids, as a benign uterine disease, lead to hysterectomies in many cases, both world-wide and in Germany [19]. The impairment of quality of life was recently investigated in a study with 968 patients [20]. The PEARL-III study presented in this work is another step in the field of medical treatment of fibroids.

Study Design

For the treatment of patients with symptomatic fibroids, the single (PEARL-III study) and repeated (up to 4x, PEARL-III extension study) intermittent administration of ulipristal acetate (UPA, 10 mg/day) over 3 months each with a treatment break of 2 menstrual cycles was investigated. An additional treatment of 10 mg norethisterone acetate per day for 10 days following each 3-month therapy cycle had no therapeutic advantage with regard to the primary and main secondary study parameters.

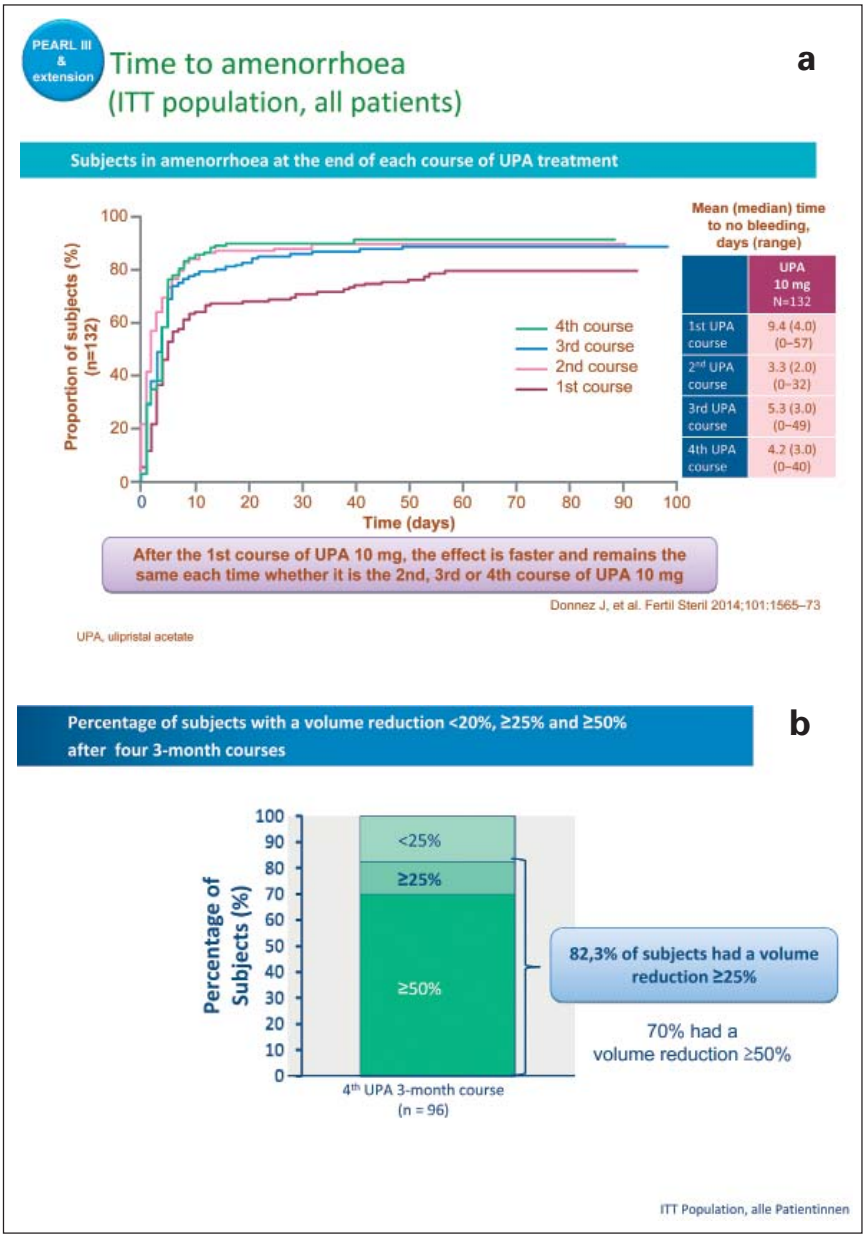

Figure 2. Results of the PEARL-III study **(a)**. Rate of amenorrhoea in symptomatic fibroid patients under therapy with UPA over 4 treatment cycles at 3 months each, followed by 10 days 10 mg NEAT or placebo and a follow-up exam. **(b)**. Reduction of fibroid volume of the 3 largest fibroids over 4 UPA treatment cycles at 3 months each, followed by 10 days 10 mg NETA/placebo and a follow-up exam. (c). Volume reduction in symptomatic fibroid patients (over 25% change in total volume of the 3 largest fibroids from baseline) over 4 UPA treatment cycles of 3 months each, followed by 10 days 10 mg NETA/placebo each and a follow-up exam. Mod. according to: J. Donnez, et al. Long-term treatment of uterine fibroids with ulipristal acetate. Fertil Steril 2014; 101: 1565–73 as well as from internal documents ("courtesy of GR/PregLem SA "). Reprint with approval of Gedeon Richter AG.

Bleeding Control

Bleeding control, in particular the occurrence of amenorrhea at the end of each UPA course, was the primary study parameter. As with the PEARL-I [14] and -II studies [15], rapid bleeding control was also observed in the PEARL-III study with the onset of amenorrhoea shortly after the start of treatment. Bleeding control could be achieved in 94% of patients, and 90% developed amenorrhoea. Furthermore, the period until bleeding control or amenorrhoea shortened with each treatment cycle.

Sufficiently high, preoperative haemoglobin values can be achieved by rapid bleeding control in addition to iron substitution therapy. This is an advantageous prerequisite in particular before surgical interventions, here for treatment of uterine leiomyoma. This statement is based on an analogy conclusion from the

study published in The Lancet, in which postoperative results were more unfavourable in major non-cardiac operations for patients with preoperative anaemia [21].

Reduction of Fibroid Volume

The secondary study endpoint was the volume reduction of the 3 largest fibroids investigated after 4 treatment cycles. This was 72% after the fourth treatment cycle. In total, 82% of patients had a volume reduction of ≥ 25%. The sustained effect on fibroid size after medication-related volume reduction proved to be an additional advantage, if the patient decided against an operation. There are comparable findings from the PEARL-II study [15]. It is assumed that UPA induces apoptosis in the uterine fibroids and inhibits the proliferation of fibroid cells. This means that a long-term intermittent UPA treatment could lead to a progressive regression of the fibroids.

Improvement in Quality of Life

The respective scores showed a clear improvement in quality of life. In 95% of the patients (treated with 10 mp UPA), an operation proved to be unnecessary during the entire study period.

Drug Safety

In comparison to the PEARL-I and -II studies, no new safety issues were detected.

For which Patients should an Intermittent Repeated UPA Treatment be Considered?

This depends on the size of the fibroid, the intensity of the bleeding and any additional symptoms. It should be taken into consideration whether repeated administration is given directly with the second menstrual period after the first treatment cycle or after an extended off-treatment interval depending on the individual situation of the patient. Both approaches are possible. For a final assessment, however, more extensive clinical experience is required.

Typical indications are:

- Women of all ages with severe symptoms, including hypermenorrhoea, caused by uterine leiomyoma that require/wish an effective medical treatment.
- Perimenopausal women who want to reach the menopause without fibroid surgery.
- Women with symptomatic uterine leiomyoma, for whom a repeated UPA 5 mg administration promises a better effect regarding surgical preparation.
- Patients with symptomatic uterine leiomyoma, good or medium response to a single UPA administration and:
  - patient wishes for a temporary delay of surgery (e. g. a stay abroad)
  - medical contraindications for surgical intervention
  - wish for further conservative therapy (in the hope of avoiding surgery or expressed in conformance with indication and reimbursement (to obtain, if applicable, an even better postoperative outcome)
  - a long time until thinking about children in the case of an assumed high rate of recurrence postoperatively e. g. in the case of virgo intacta and/or very young patients
  - if applicable, in the case of a desire for children in older patients with ovarian "low response" and fibroids which do not impair the cavum and a negative attitude towards surgery (case-by-case decision).

The effect of UPA in patients planning a pregnancy without an operation following treatment of uterine leiomyoma vs. an operation alone regarding pregnancy and the baby take home rate is still unclear. This question would have to be researched in a randomised study on "UPA and operation vs. UPA without operation".

Multiple treatments can be considered since it has been approved by the EMA, based on the results of the PEARL-IV study.

Therapeutic Options after UPA Treatment

At the end of a UPA treatment, there is the question of necessity of a fibroid surgery, operability with various surgical techniques (laparascopic, per laparotomiam, hysteroscopic, radiological by embolisation or focussed ultrasound), dependent on age, medical surgical risk, the location and size of the fibroid, any additional symptoms such as urinary incontinence and descent complaints, as well as a desire for children and contraception. Finally, the question of to what extent fibroid surgery is easier or more difficult with endoscopic interventions, has not yet been clarified anywhere in the world. Jacques Donnez has reported many times at congresses that he has never had a problem with the preparation of fibroids after UPA treatment during laparoscopic surgery – this had been reported in the past for operations after pre-treatment with GnRH analogues [22].

To date, there have been no studies exploring how long one should wait after a UPA treatment until surgical interventions or reproductive medicinal therapies are performed. Regarding this, there are only personal and empirical data which were published by Römer et al. in the form of lectures. Thus, hysteroscopic fibroid surgery should take place, due to a possible endometrial thickening, after 2 menstrual periods or, without endometrial thickening, directly after therapy. A laparoscopic or laparotomic operation or radiological intervention is possible directly after UPA treatment. For patients planning to get pregnant, case reports of spontaneous pregnancies after the end of therapy have been published. At least one menstrual period between end of treatment and pregnancy attempts would be preferred. Before IVF treatment, the patient should have two periods after UPA pre-treatment, as there are currently no data on the influence of UPA treatment on the implantation capability of the endometrium.

Approval Status

Approval text until 1/2014

Ulipristal acetate is indicated for pre-operative treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age. The duration of treatment is limited to 3 months.

The treatment consists of one tablet of 5 mg to be taken orally once daily for up to 3 months.

Treatment should be started during the first week of a menstrual cycle.

There are no data available on treatment with a duration longer than 3 months or on repeat courses of treatment, therefore, treatment duration should not exceed 3 months.

Extended indication since January 2014

With the amendment to the approval since January 2014, the text had been

changed to: Ulipristal acetate is indicated for preoperative treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age. The treatment consists of one tablet of 5 mg to be taken orally once daily for up to 3 months. This 3-month treatment course can be repeated once. Re-treatment should start at the earliest during the second menstruation following the first treatment course completion.

The two current indications since May 2015

With the most recent extension of the indication in May 2015 UPA has been approved for the following two indications:

- Ulipristal acetate is indicated for preoperative treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age.
- Ulipristal acetate is indicated for intermittent treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age.

The treatment consists of one tablet of 5 mg to be taken orally once daily for up to 3 months.

This 3-month treatment course can be repeated as often as required by patient's symptoms. Re-treatment should start at the earliest during the second menstruation following the first treatment course completion.

The Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) has adopted a positive opinion on the company's application to extend the indication of Esmya® 5 mg tablets (ulipristal acetate) to the long-term repeated intermittent treatment of moderate to severe symptoms of uterine fibroids on 23 April 2015.

The CHMP positive opinion has been forwarded to the European Commission, which amended the EU marketing authorisation for Esmya® 5 mg applicable to all countries of European Union, and gave final approval for both indications in May 2015.

PEARL-IV study

The PEARL-IV study will have to demonstrate, in addition to the PEARL-III and PEARL-III extension studies, the clinical advantages of a long-term interval therapy on bleeding control, fibroid size and quality of life. Part I of this study with data for 2 cycles of UPA treatment has been published in January 2015, the full publication with all 4 cycles is expected later this year.

Internet Links

- Esmya®: www.esmya.de; www.myom-wissen.de
- EMA press release: http://www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion/human/002041/WC500186173.pdf
- Gedeon Richter England: http://www.fibroidsconnect.com
- myhealth Alberta: https://myhealth.alberta.ca/health/Pages/conditions.aspx?hwid=tv7261
- WebMed: http://www.webmd.com/women/uterine-fibroids/uterine-fibroids
- PubMed Health: http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0001912
- UK Patient: http://www.patient.co.uk/health/fibroids-leaflet
- Geneva Medical Foundation: http://www.gfmer.ch/Guidelines/Gynecology/Uterine_fibroids.htm
- Fibroid Foundation: http://fibroidfoundation.org/archives/109
- Mayo Clinic (USA): http://article.wn.com/view/2013/10/25/Mayo_Clinic_Study_Uterine_Fibroids_Have_Significant_Impact_o

Conflicts of Interest

H. J. Ahrendt carries out further training for Gedeon Richter, C. Albring denies a conflict of interests, J. Bitzer is scientific advisor for Gedeon Richter, Switzerland, M. Bohlmann received a lecture fee in 2013 from Gedeon Richter, C. Egarter received lecture and study fees from Gedeon Richter, K. König denies a conflict of interests, A. O. Mueck denies a conflict of interests, K. Peters has received grants for carrying out a study from Gedeon Richter and participation on the advisory board, T. Rabe received fees for lectures, publications and participation on the advisory board from Gedeon Richter, T. Römer received fees for lectures and consultancy work from Gedeon Richter, N. Sänger is a consultant for Gedeon Richter, H. R. Tinneberg received fees for lectures from Gedeon Richter, M. Wallwiener denies a conflict of interests.

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