EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 April 2015
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Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Esmya

International non-proprietary name: ULIPRISTAL

Procedure No. EMEA/H/C/002041/II/0028

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5520
Send a question via our website www.ema.europa.eu/contact

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List of abbreviations

ACTH	Adrenocorticotropic hormone
ADR	Adverse drug reaction
AE	Adverse event
ALT	Alanine transaminase
AST	Aspartate transaminase
BMI	Body mass index
E2	Oestradiol
ECG	Electrocardiogram
EMA	European Medicines Agency
FDA	Food and Drug Administration
Fe2+	Iron
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GnRH	Gonadotropin releasing hormone
Hb	Haemoglobin
Hct	Haematocrit
ICF	Informed consent form
ICH	International Conference on Harmonization
INR	International normalized ratio
ITT	Intent-to-treat
LCL	Lower confidence limit
LDH	Lactate dehydrogenase
LDL	Low density lipoprotein
LH	Luteinising hormone
MAA	Marketing Authorisation Application
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
NETA	Norethisterone acetate
NICHD	National Institute of Child Health and Human Development
NIH	National Institutes of Health
P4	Progesterone
PAEC	Progesterone Receptor Modulator Associated Endometrial Changes
PBAC	Pictorial Bleeding Assessment Chart
PEARL	Study short name for: PGL4001 (ulipristal acetate) Efficacy Assessment in Reduction of Uterine Leiomyomata
PK	Pharmacokinetic

PIP	Paediatric investigational plan
PP	Per-protocol
PR	Progesterone receptor
PRM	Progesterone Receptor Modulator
QoL	Quality of life
RMP	Risk Management Plan
RTI	Research Triangle Institute
SAE	Serious adverse event
SD	Standard deviation
SF-MPQ	Short Form McGill Pain Questionnaire
SOC	System organ class
SmPC	Summary of Product Characteristics
SPRM	Selective Progesterone Receptor Modulator
TEAE	Treatment emergent adverse event
TSH	Thyroid-stimulating hormone
UFS-QoL	Uterine Fibroid Symptom and Health-Related Quality of Life Questionnaire
ULN	Upper limit of normal range
VAS	Visual Analogue Scale

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Gedeon Richter Plc. submitted to the European Medicines Agency on 6 August 2014 an application for a variation.

This application concerns the following medicinal product:

Centrally authorised Medicinal product(s): **For presentations: See Annex A**	**International non-proprietary name:**
Esmya	ULIPRISTAL

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II and IIIB

The Marketing authorisation holder (MAH) applied for an extension of the indication to include intermittent treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age. Consequently, the MAH proposed the update of sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC.

The Package Leaflet was proposed to be updated in accordance. Furthermore, the key elements of the educational material in Annex II have been updated.

The variation proposed amendments to the Summary of Product Characteristics, Annex II and Package Leaflet

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/215/2009 on the granting of a product-specific waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The applicant did not seek scientific advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:

Rapporteur: Kristina Dunder Co-Rapporteur: Pieter de Graeff

Timetable	Actual dates
Submission date	6 August 2014
Start of procedure:	22 August 2014
CHMP Co-Rapporteur Assessment Report	13 October 2014
CHMP Rapporteur Assessment Report	13 October 2014
PRAC Rapporteur Assessment Report	21 October 2014
PRAC Rapporteur Updated Assessment Report	4 November 2014
PRAC Meeting, adoption of PRAC AR	6 November 2014
CHMP Rapporteur Updated Assessment Report	14 November 2014
Request for supplementary information (RSI)	20 November 2014
PRAC Rapporteur Assessment Report	28 January 2015
CHMP Rapporteur Assessment Report	26 January 2015
PRAC Rapporteur Updated Assessment Report	09 February 2015
PRAC Meeting, adoption of PRAC AR	12 February 2015
CHMP Rapporteur Updated Assessment Report	23 February 2015
2nd Request for supplementary information (RSI)	26 February 2015
PRAC Rapporteur Assessment Report	1 April 2015
CHMP Rapporteur Assessment Report	1 April 2015
PRAC Meeting, adoption of PRAC AR	10 April 2015
CHMP Rapporteur Updated Assessment Report	17 April 2015
Opinion	23 April 2015

2. Scientific discussion

2.1. Introduction

Problem statement

Uterine fibroids (uterine leiomyoma) are benign, monoclonal, hormone-sensitive, smooth muscle tumours of the uterus. They are the most common tumour of the female reproductive tract in pre-menopausal women and have been reported to affect 20-40% of women during their reproductive years.

Uterine fibroids are often asymptomatic, but when symptomatic, the primary symptoms are heavy uterine bleeding, anaemia, abdominal pressure, abdominal pain, increased urinary frequency and infertility. In particular, heavy menstrual blood loss is one of the most frequently disabling symptoms of uterine fibroids.

Uterine fibroids are commonly treated surgically. Symptomatic uterine fibroids are the leading reason for hysterectomy. Other, less invasive treatment procedures include myomectomy (which may preserve fertility), uterine artery embolization and, if the dominant symptom is bleeding, endometrial ablation.

Medical treatments of symptomatic fibroids are currently limited to short-term use prior to surgery and comprise either progesterone receptor modulators, i.e. ulipristal acetate (Esmya) or gonadotropin releasing hormone (GnRH) agonists.

GnRH-agonists are effective in reducing fibroid-related bleeding, correcting anaemia when given concomitantly with iron therapy, reducing abdominal symptoms and reducing fibroid and uterine volume. Their use is limited to 3-6 months duration as suppression of oestrogen to castration levels results in menopausal symptoms including hot flushes, mood swings and loss of libido and can also lead to loss of bone mineral density.

Ulipristal acetate 5 mg tablets (Esmya) is currently approved for pre-operative use with a posology restricted to two intermittent treatment courses of 3 months due to absence of long-term safety data.

Surgery may not be a suitable option for all patients, e.g. for medical or personal reasons or if the woman is peri-menopausal and would rather wait that the symptoms of uterine fibroids decrease as result of menopause. Thus, a long-term medical treatment of fibroids would be valuable.

About the product

Esmya (ulipristal acetate) is an orally-active, synthetic selective progesterone receptor modulator characterised by a tissue-specific partial progesterone antagonist effect. Each tablet contains 5 mg of ulipristal acetate.

Esmya was granted EU Marketing Authorisation on 23 February 2012 for the pre-operative treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age with a treatment duration limited to 3 months. The duration of treatment was limited to one course of 3 months which was due to the absence of long term safety data for a period longer than 3 months or on repeat courses of treatment.

Subsequently the indication was extended to allow two 3-month treatment courses if deemed appropriate by the treating physician (variation EMEA/H/C/2041/II/19, EC Decision on 18 December 2013). This was based on the results of PGL09-027 and PGL09-026 studies (respectively PEARL III extension and PEARL III) which investigated the safety and efficacy of up to four 3-month treatment courses of ulipristal acetate 10 mg.

The present variation application is to extend the indication to allow repeated intermittent treatment courses in women who are not planned to undergo surgery.

The indication applied for was: “Ulipristal acetate is indicated for long term (repeated intermittent) treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age.”

The indication recommended is: “Ulipristal acetate is indicated for intermittent treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age” (see SmPC section 4.1)

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

Treatments should only be initiated when menstruation has occurred:

- The first treatment course should start during the first week of menstruation.

- Re-treatment courses should start at the earliest during the first week of the second menstruation following the previous treatment course completion.

The treating physician should explain to the patient the requirement for treatment free intervals.

Repeated intermittent treatment has been studied up to 4 intermittent courses (see SmPC section 4.2).

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity / environmental risk assessment

Based on the CHMP Guideline on the Environmental Risk Assessment of Medicinal products for Human Use (EMEA/CHMP/SWP/4447/00, 1 June 2006), an action limit is in principle not applicable for ulipristal acetate, as it is a selective progesterone receptor modulator and a potential endocrine disruptor.

At the time of marketing authorisation, the calculated concentration for PECsurface water was estimated to be less than the 0.01 µg/L threshold value. Based on the extensive metabolism and very limited excretion of unchanged ulipristal, its therapeutic use is unlikely to represent a risk to the environment. However, a Phase II environmental risk assessment was recommended, and underway, to further characterise the potential endocrine modulating properties of ulipristal acetate in the environment.

In the context of the obligation of the MAH to take due account of technical and scientific progress, the CHMP has recommended the following points to be addressed:

- a phase II ERA for ulipristal acetate.

Results of the ongoing fish-full life-cycle (FFLC) study which is part of the Environmental Risk Assessment (ERA) phase II program are expected early Q2 2015.

2.2.2. Conclusion on the non-clinical aspects

In the context of the obligation of the MAH to take due account of technical and scientific progress, the CHMP recommends the following points for further investigation:

- a phase II ERA for ulipristal acetate including a fish-full life-cycle (FFLC) study

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Table 1: Efficacy study design characteristics of completed studies

Phase	Study	Design	Treatment Duration	Treatment groups	Dose	Number of subjects
III	PGL07-021 (PEARL I)	Double-blind, placebo controlled	12-13 weeks[a]	Ulipristal acetate[b]	5 mg/day	96
					10 mg/day	98
				Placebo[b]	-	48
	PGL07-022 (PEARL II)	Double-blind, double-dummy, active comparator controlled	12-13 weeks[a]	Ulipristal acetate	5 mg/day	102
					10 mg/day	103
				Leuprorelin	3.75 mg once a month[c]	202
	PGL09-026 (PEARL III)	Open Label for ulipristal acetate	90 days	Ulipristal acetate[d]	10 mg/day	209
	PGL09-027 (PEARL III extension)	Open Label for ulipristal acetate	additional 3 x 90 days[e]	Ulipristal acetate[d]	10 mg/day	132
	PGL11-006 (PEARL IV)	Double-blind parallel group	4 x 84 days[e]	Ulipristal acetate	5 mg/day	228
					10 mg/day	223
II	PGL-N-0287	Double-blind, placebo controlled	12 weeks	Ulipristal acetate	10 mg/day	8
					20 mg/day	6
				Placebo	-	8
	PGL-N-0090	Double-blind, placebo controlled	12-24 weeks[f]	Ulipristal acetate	10 mg/day	14
					20 mg/day	14
				Placebo	-	13

a with a 6 months safety follow-up.

b 80 mg Fe^{2+} (Tardyferon, containing 256.3mg of ferrous sulfate, equivalent to 80mg of Fe^{2+}) was administered daily, concomitantly in all treatment groups

c Administered as an intramuscular injection

d after 90 days of ulipristal acetate treatment, all subjects were randomized to receive a treatment of 10 days of 10 mg of NETA or placebo.

e treatment courses were separated by a drug free interval of approximately 6 weeks.

f Week 12 to PEARL III as an optional, unblinded extension period of ulipristal acetate treatment, which was undertaken by 4 subjects from the placebo group (2 each received ulipristal acetate 10 and 20 mg/day), 3 subjects in the ulipristal acetate 10 mg/day group and 6 subjects in the ulipristal acetate 20 mg/day group

Short-term efficacy of ulipristal acetate was investigated in previously submitted studies, evaluating pre-operative treatment of uterine fibroids:

- Two short-term Phase III studies (Study PGL07-021 and Study PGL07-022),
- Two smaller Phase II studies (Study PGL-N-0287 and Study PGL-N-0090)

A further Phase III study, PGL09-026, evaluated the efficacy of a 3-month course of ulipristal acetate 10 mg once daily.

The efficacy of ulipristal acetate as a long-term treatment of uterine fibroids has been assessed in two long-term Phase III studies which are submitted in support of this extension of indication:

- The above mentioned Study **PGL09-026** and its extension **PGL09-027** assessed the efficacy and safety of ulipristal acetate 10 mg over a total of 4 intermittent 3-month treatment courses
- Study **PGL11-006** assessed the efficacy and safety of ulipristal acetate 5 and 10 mg over a total of 4 intermittent 3-month treatment courses.

2.4. Clinical pharmacology

No additional clinical pharmacology data have been submitted within this variation which was considered acceptable by CHMP considering the applied extension of indication.

2.5. Clinical efficacy

The present application is based on the results from study PGL11-006 (Clinical study report covering Part I of this study dated 28 May 2014, with the results of the first 2 treatment courses; Clinical study report covering Part II dated 12 March 2015 including results of courses 3 and 4).

In addition, some results from the previously assessed study PGL09-027 (see variation application EMEA/H/C/2041/II/19) have also been presented. Study PGL09-027 was a Phase III, multicentre, clinical study investigating the efficacy and safety of three successive courses of 3-month open-label ulipristal acetate treatment, each followed by ten days of double-blind treatment with progestin or placebo and a drug-free period until return of menses, in subjects with myomas and heavy uterine bleeding. Study PGL09-027 was the optional extension to study PGL09-026. The main objective of this extension study was to assess the sustained efficacy and safety of long term on-off treatment with Esmya on uterine bleeding, myoma size, pain and quality of life. The study consisted of 3 further courses of 3 months open-label Esmya treatment, each followed by 10 days of double-blind treatment with Norethisterone acetate (NETA) or placebo, and then a drug-free period.

2.5.1. Main study

Study PGL11-006

This was a Phase III, multicentre, randomised, double-blind clinical study, investigating the efficacy and safety of repeated 12-week courses of daily 5 mg or 10 mg doses of ulipristal acetate for the long-term management of symptomatic uterine fibroids.

Methods

Study participants

The study population consisted of pre-menopausal women with symptomatic uterus myoma(s) characterised by heavy bleeding. Patients had to have the required severity of symptoms, i.e. Pictorial Bleeding Assessment Chart (PBAC) score >100, but with no condition that was so severe that emergency surgery would have been required within 3 months regardless of any treatment impact.

Key inclusion criteria are outlined below:

- Pre-menopausal women between 18 and 50 years inclusive.
- Patient with a Body Mass Index ≥18 and ≤40.
- Patient with hormonal levels of follicle stimulating hormone (FSH) ≤20 mIU/mL (measured at the screening 2).
- Patient with myomatous uterus <16 weeks (compared to a uterus of 16 weeks of pregnancy).
- Patient with a largest uterine myoma between 3 cm and 12 cm diameter inclusive.
- Patient with menstrual cycle ≥22 and ≤35 days. The menstrual cycle between screening 1 and visit 2 was the one considered for assessing eligibility.

– Pictorial Bleeding Assessment Chart (PBAC) score >100 as measured during screening over the first 8 days of the menstrual bleed.

– Patient had no significant findings at breast examination at the screening visit.

Females of childbearing potential were advised to practice a non-hormonal method of contraception (sexual abstinence, diaphragm, condom or having a partner with a vasectomy with either confirmed azoospermia or performed at least 6 months prior to the study)

Females of non-childbearing potential were defined as women with tubal ligation sterilisation at least 2 months before the start.

Key exclusion criteria are outlined below:

– The patient had a history of uterus surgery that would interfere with the study endpoints (as assessed by the Investigator). Subjects who had a uterine artery embolisation may be included ≥6 months after the procedure.

– The patient had a history of or current uterus, cervix, ovarian or breast cancer.

– The patient had had a significant and persisting finding on Papanikolaou test (PAP) smear within the past 12 months.

– The patient had a history of endometrium hyperplasia or adenocarcinoma or similar lesions in the screening biopsy. If by exception the endometrium biopsy results were only made available after the subject's visit 2, the Investigator followed certain instructions listed in the protocol.

– Patient had a large uterine polyp (>2 cm).

– Patient had extensively calcified myomas and/or uterus.

– Patient had a known severe coagulation disorder.

– Patient had one or more ovarian cysts ≥4 cm diagnosed by ultrasound (US).

– The patient had a history of treatment for myoma with a SPRM.

– The patient had been taking prohibited medication:

  o Treatments with progestins (systemic or progestin releasing intra-uterine system) or an oral contraceptive within the month before the screening visit

  o Acetylsalicylic acid, mefenamic acid, anticoagulants such as coumarins and/or antifibrinolytic drugs such as tranexamic acid within 1 week before the screening visit

  o Systemic glucocorticoid treatments and/or systemic depot glucocorticoid treatments within 1 week or 2 months before the screening visit, respectively.

  o Gonadotropin Releasing Hormone (GnRH) agonist and antagonist:

    - immediate or monthly sustained release depot preparation or immediate release form within 6 months of screening visit

    - 3 or 6 months sustained release depot preparation within 12 months before the screening visit.

– The patient was likely to require treatment during the study with drugs that were not permitted by the study protocol: progestins (systemic or progestin releasing intra-uterine system), hormonal contraceptives, systemic glucocorticoids (oral and injectable), GnRH agonist and GnRH antagonists.

– The patient required treatment with a medication which included potent inhibitors of cytochrome P450 (CYP)3A4 (such as ketoconazole) or potent inducers of CYP3A4 (such as rifampicin).

– The patient had abnormal hepatic function at study entry (defined as aspartate transaminase [AST], alanine transaminase [ALT], gamma-glutamyl transferase [GGT], hepatic alkaline phosphatase, or total bilirubin above twice the upper limit of normal). In case of isolated elevated GGT, the subject could be enrolled if the re-test was within the allowed limits.

– The patient had a positive pregnancy test at baseline, was nursing or planning a pregnancy during the course of the study.

Treatments

There were two parallel arms in the study:

- PGL4001 (ulipristal acetate) 5 mg daily administration (PGL4001 5 mg + placebo of the PGL4001 10 mg tablet)
- PGL4001 (ulipristal acetate) 10 mg daily administration (PGL4001 10 mg + placebo of the PGL4001 5 mg tablet)

Each treatment course lasted 12 weeks (84 days). Treatment courses were separated by a drug-free period until the start of the second menstruation following the end of the previous treatment course. There were 4 treatment courses in total.

The clinical study report for Part I presented data after completion of treatment courses 1 and 2, up to visit 8.

The final clinical study report (Part II) presented data after completion of all four treatment courses, up to visit 12.

The study design is outlined below (Figure 1).

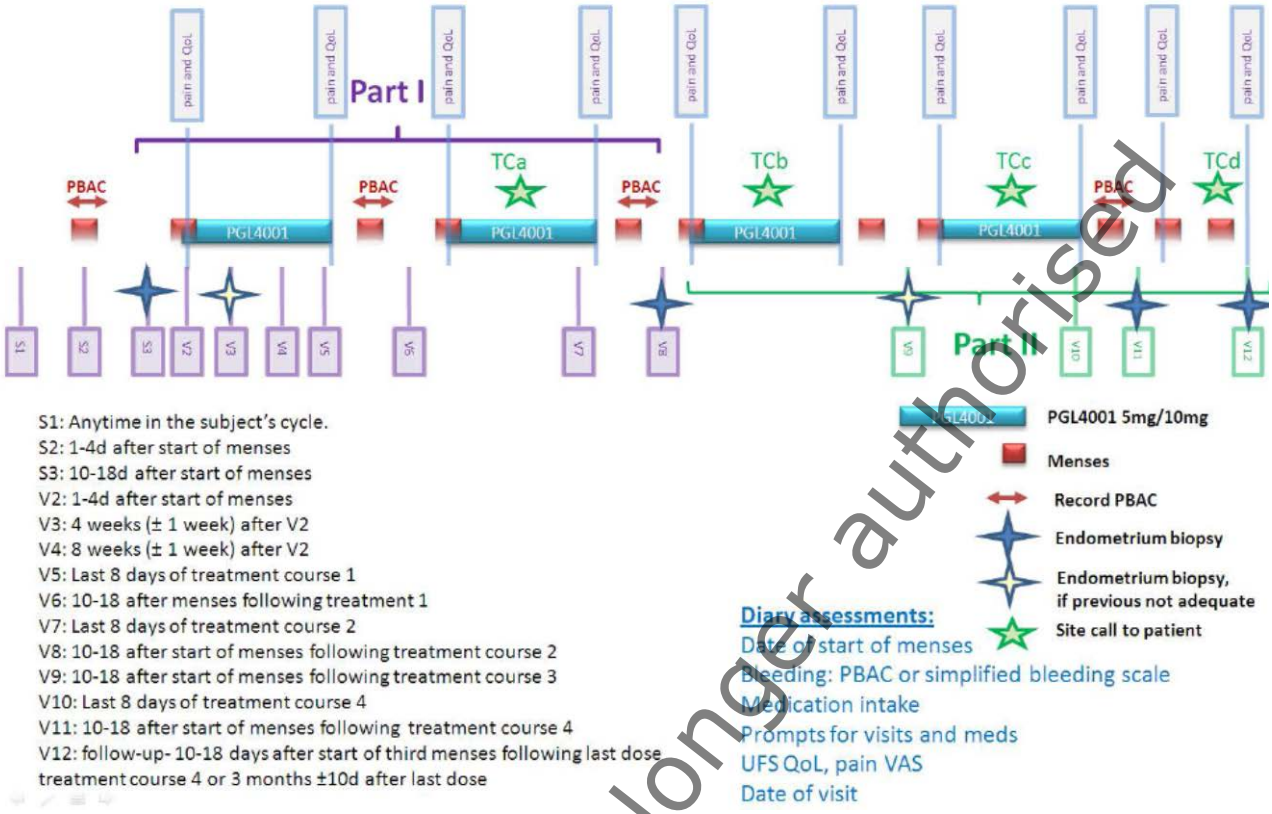

Figure 1: PEARL IV (PGL11-006) Study Design

Patients started the 12 week PGL4001 treatment (treatment course 1) at visit 2, which took place within the first 4 days of the start of menstruation following completion of screening assessments. At visit 6 (between 10 and 18 days after the first day of the first menstruation following the end of treatment course 1), PGL4001 treatment course 2 was dispensed and patients were instructed to start taking the medication on the first or second day of their next menstruation. At visits 8 and 9 (between 10 and 18 days after the first day of the first menstruation following the end of treatment courses 2 and 3 respectively), PGL4001 treatment courses 3 and 4, respectively, were dispensed and patients were instructed to start taking the medication on the first or second day of their next menstruation.

Objectives

Part I:

The primary objective was to compare and assess the sustained efficacy of two repeated 12-week treatment courses of daily administration of 5 mg and 10 mg doses of PGL4001 on uterine bleeding in women with uterine fibroids.

Secondary efficacy objectives were to compare and assess the sustained efficacy of two repeated 12-week treatment courses of daily administration of 5 mg and 10 mg doses of PGL4001 on myoma volume, uterus volume, Quality of Life (QoL) and pain.

A number of exploratory objectives were also included, e.g.

- To assess uterine bleeding characteristics (timing and amount of blood loss) upon return of menses following treatment course 1.

- To assess uterine bleeding characteristics (timing and amount of blood loss) upon return of menses following treatment course 2.
- To assess the histology of the endometrium, including PAECs, 10-18 days after start of menstruation following the completion of the second course of PGL4001 treatment.
- To assess the change from baseline to the start of the second menstruation after the end of treatment course 1 in QoL (measured with UFS-QoL) and pain.
- To assess the incidence and type of surgery on fibroids.

Part II:

The primary objective was to compare and assess the sustained efficacy of four repeated 12-week treatment courses of daily administration of 5 mg and 10 mg doses of PGL4001 on uterine bleeding in women with uterine fibroids

Secondary efficacy objectives were to compare and assess the sustained efficacy of four repeated 12-week treatment courses of daily administration of 5 mg and 10 mg doses of PGL4001 on myoma volume, uterus volume, Quality of Life (QoL) and pain.

A number of exploratory objectives were also included, e.g.

- To assess the timing of return of menses following PGL4001 treatment course 3.
- To assess uterine bleeding characteristics (timing and amount of blood loss) upon return of menses following treatment course 4.
- To assess the histology of the endometrium, including PAECs, 10-18 days after start of menstruation following the completion of the fourth course of PGL4001 treatment.
- To assess the change from baseline to the start of the second menstruation after the end of treatment courses 2, 3 and 4 and to the end of study visit in QoL (measured with the UFS QoL) and pain.
- To assess the change from baseline to the end of study visit in QoL (measured with EuroQol Group Health Outcomes Questionnaire of 5 Dimensions [EQ-5D]).
- To assess the incidence and type of surgery on fibroids.

Secondary safety objectives were to assess the overall safety of two (Part I) and four (Part II) repeated 12-week treatment courses of daily administration of 5 mg or 10 mg doses of PGL4001 respectively.

Outcomes / endpoints

Efficacy Measurements

- Uterine bleeding pattern

The primary efficacy endpoint was the percentage of patients who are in amenorrhoea at the end of both treatment courses 1 and 2 (Part I) and at the end of all treatment courses (Part II). Amenorrhoea was defined as no more than 1 day of spotting within a 35-day interval.

Patients recorded their bleeding pattern in their diary using an 8-day PBAC at screening, when a score of >100 was required for inclusion, and after the first, second and fourth treatment courses. In total, patients were expected to complete the PBAC for 32 days (4 x 8 days). Bleeding occurring outside of the timeframe described above was recorded in the subject diary in a simplified semi-quantitative bleeding pattern containing 4 categories defined as “no bleeding”, “spotting”, “bleeding” or “heavy bleeding”.

A large number of secondary end-points (Part I and Part II) were also related to the bleeding pattern, e.g.:

– Percentage of subjects in amenorrhoea at the end of treatment course 1, 2, 3 and 4, respectively

– Percentage of subjects in amenorrhoea in the last 56 days of treatment course 1, 2, 3 and 4, respectively

– Proportion of days with uterine bleeding between visit 2 and visit 8 (Part I), between visit 2 and visit 11 (Part II)

– Proportion of days with heavy uterine bleeding between visit 2 and visit 8 (Part I), between visit 2 and visit 11 (Part II)

– Median time to amenorrhoea during treatment course 1, course 2, course 3 and course 4 respectively

- Myoma volume

Change from baseline to visits 6, 7 and 8 (Part I) or to visits 9, 10, 11 and 12 (Part II) in the volume of the three largest myomas and in uterus volume, measured by transvaginal US were secondary efficacy end-points in Part I.

Total volume of the 3 largest myomas and uterine volume were measured at screening 3 and visits 6, 7, 8, 9, 10, 11 and 12. If possible, the US was performed by the same assessor at each visit.

- Pain

Change from baseline to end of treatment course 1 and course 2 (Part I) and to treatment course 3 and course 4 (Part II), respectively, in pain measured by VAS (Visual Analogue Scale) were secondary end-points. VAS was recorded in diaries at the start and end of each treatment course, at the start of the second menses after treatment course 4 and at visit 12. A Pain VAS score of 0 represented no pain and a score of 100 represented worst possible pain.

- Quality of life

Other secondary endpoints were change from baseline to end of treatment course 1 and course 2 (Part I) and course 3 and course 4 (Part II), respectively in QoL. QoL was measured using the specific UFS-QoL symptom severity score (Measurement of Discomfort due to Uterine Fibroids) and HRQL scales, and also by the general EQ-5D questionnaire (a general QoL scale used in several conditions).

Safety Measurements

- Endometrial thickness

A transvaginal ultrasound, during which the endometrial thickness was measured (mm), was performed at screening 3 and visits 6 to 12. If possible, the transvaginal US was performed by the same operator at the appropriate visits.

- Endometrium biopsy

The sample collection of endometrial tissue was performed by a gynaecologist at screening (screening 3), at visit 3 (only if screening biopsy was “not adequate”), after 2 treatment courses (at visit 8), at visit 9 (only if biopsy was “not adequate” at visit 8), after 4 treatment courses (visit 11) and 3 months after last dose (visit 12).

- Other safety assessments

Apart from the endometrial assessments by ultrasound and biopsies, conventional safety assessments were made, e.g. vital sign measurements and electrocardiogram, laboratory safety examinations (including serum levels of estradiol, thyroid stimulating hormone, follicle stimulating hormone and haematology, coagulation, biochemistry and lipid parameters) as well as adverse event reporting and collection (including

the above mentioned assessments, gynaecological and breast examination, any other specific assessments and subjects reporting of AEs).

Sample size

The sample size of this study was based on assessing both the efficacy and safety of long-term treatment of PGL4001. A sample size of 200 subjects per treatment arm results in the study having a power greater than 85% to detect an absolute difference in the primary endpoint between 2 treatment groups of 14% (that is, 68% versus 82%) or greater, using a 2-sided test conducted at a type I error rate of 5%. This was deemed sensitive enough, as in the absence of treatment the expected occurrence of the primary endpoint would be close to zero. In addition, the sample size calculated for the efficacy endpoint was deemed adequate in order to assess the safety of long-term treatment.

Myoma volume was also taken into consideration and the analysis was conducted after log transformation of the data, with the corresponding results back-transformed. Assuming a between-subject standard deviation of 0.6 on the log scale, a sample size of 200 subjects per treatment arm results in the study having a power of 85% to detect a ratio of average myoma volume for PGL4001 10 mg compared to PGL4001 5 mg of 0.66 or less.

Assuming a drop-out rate of approximately 10% based on previous studies, the objective was to randomise 444 subjects in order to have 400 subjects who complete 2 treatment courses.

Randomisation

At visit 2, eligible subjects were randomised to either PGL4001 5 mg or PGL4001 10 mg in a 1:1 ratio via centralized Interactive Voice/Web Response System (IVRS/IWRS). The randomisation scheme is stratified by site. Subjects were randomised into blocks of a predetermined length.

Blinding (masking)

The PGL4001 5 mg or 10 mg treatment was allocated randomly in a double-blind design. The 5 mg tablets had a 150 mg fill weight while the 10 mg tablets had a 300 mg fill weight. The blind was maintained by administering daily to each subject a tablet of 150 mg together with a tablet of 300 mg, by using matching placebo of 150 mg and 300 mg fill weight.

The study blind was maintained until the lock of the Part I database (up to and including visit 8 for all subjects). Once the Part I database was locked, the randomisation code was broken in order for the Part I analyses to be performed. Only the Sponsor and MDSL International statistics and data management personnel were therefore unblinded at this point.

Investigators, monitors, pathologists and subjects remain blinded until the Part II database has been cleaned and locked.

Statistical methods

Population for main analyses

Efficacy analyses were conducted on the Full Analysis Set 1 (FAS 1) and the PP population sets. FAS 1 population was defined as all randomised subjects who received study medication at least once during treatment course 1. Analysis of primary efficacy endpoints and myoma volume was also conducted on FAS 2, 3 and 4 (i.e. randomised subjects who received study medication at least once during treatment course 2, 3 and 4 respectively). Subjects in the FAS 1 population were analysed according to the treatment group to which they were randomised, rather than by the actual treatment they received. PP population sets were defined for each treatment course as all subjects who had not withdrawn prior to receiving at least 56 days (i.e. 2 months or 2x28 days) of ulipristal acetate treatment during the specific treatment course and had not

reported any major protocol deviations up to the start of the next treatment course or prior to study withdrawal.

Imputation rules for uterine bleeding endpoints

As bleeding monitoring by either a PBAC score or daily diary card was conducted for an extensive period of time (up to approximately 21 months), rules were defined to deal with occasional missing information. Despite the long duration of the study, for the FAS 1, 63.0% subjects had sufficient uterine bleeding data to allow assessment of the primary endpoint using observed data only. Imputation rules applied to the daily uterine bleeding pattern, amenorrhoea and controlled bleeding assessments are; if three consecutive days or less of the daily uterine bleeding pattern are missing, the values for the missing days will be imputed with the greatest strength of bleeding immediately before or after the period of missing days. For example, if a subject records 'Heavy Bleeding' then has two missing days followed by 'Spotting', the missing days will be imputed as 'Heavy Bleeding'. If more than three consecutive days of the daily uterine bleeding pattern are missing, the values for the missing days will not be imputed. If a subject has more than three consecutive missing days in the last 35 days of a treatment course the amenorrhoea assessment will therefore be missing, unless the subject has reported at least two days of spotting or at least one day of bleeding/heavy bleeding in the last 35 days of the treatment course in question (subject is not in amenorrhoea).

Imputation due to early discontinuation

If a subject withdrew prior to completing a treatment course then:

• the amenorrhoea assessment was imputed as a failure (subject was not in amenorrhoea) for the treatment course in question (if the amenorrhoea assessment was missing for that course), and for any subsequent course that had not been started for subjects where the primary reason for withdrawal was deemed negative, i.e. a treatment failure. Negative reasons for withdrawal included, but were not limited to, AE, protocol deviation and lack of efficacy.

• the amenorrhoea assessment was imputed as a success (subject was in amenorrhoea) for the treatment course in question (if the amenorrhoea assessment was missing for that course), and for any subsequent course that had not been started if the primary reason for withdrawal was deemed positive. Positive reasons for withdrawal included, but were not limited to, subject request: wished pregnancy and subject request: symptoms so much better that no longer continued on treatment.

Primary Efficacy Analyses

All statistical hypothesis tests and CIs were two sided, using a 5% level of statistical significance.

The results obtained with the two doses of ulipristal acetate (5 mg and 10 mg) were compared using a continuity-adjusted chi-squared test. The confidence interval for the difference between PGL4001 5mg and PGL4001 10mg are presented using the Newcombe-Wilson score method.

Secondary Efficacy Analyses

The secondary endpoints of percentage or proportions were analysed using the same method employed for the primary analysis.

The median time to amenorrhoea during each treatment course was analysed using Kaplan-Meier methods.

Changes from baseline to each treatment course in quality of life measured with the UFS-QoL questionnaire, EQ-5D VAS scores and pain measured by VAS were analysed using an ANCOVA model with terms for treatment, treatment course, baseline value and the following interactions: treatment course x treatment, treatment course x baseline. The covariance among the repeated measures was modelled separately as unstructured. From the resulting model, estimates of the mean change with the two doses of ulipristal acetate were compared, and CIs and p-values were presented for the end of each treatment course. Shift

tables showing changes from baseline were presented for each of the 5 dimensions of the EQ-5D questionnaire. The number and percentage of subjects whose pain improved by at least 30% and 50% were summarised by time point, and a subgroup analysis of the most severe subjects at baseline (VAS >40) was performed.

Changes in fibroid volume and in uterine volume were analysed with a repeated measures ANCOVA model. Data were log-transformed before analysis and subsequently back-transformed prior to presentation. The ANCOVA model included the log total fibroid/uterine volume as the dependent variable and terms for treatment, visit, log total fibroid/uterine volume at screening and the following interactions: visit x treatment, visit x log total fibroid/uterine volume at screening. The covariance among the repeated measures was modelled separately as unstructured.

Results

Participant flow

A total of 555 subjects were screened at 46 sites in 11 countries, and of these 451 were randomised.

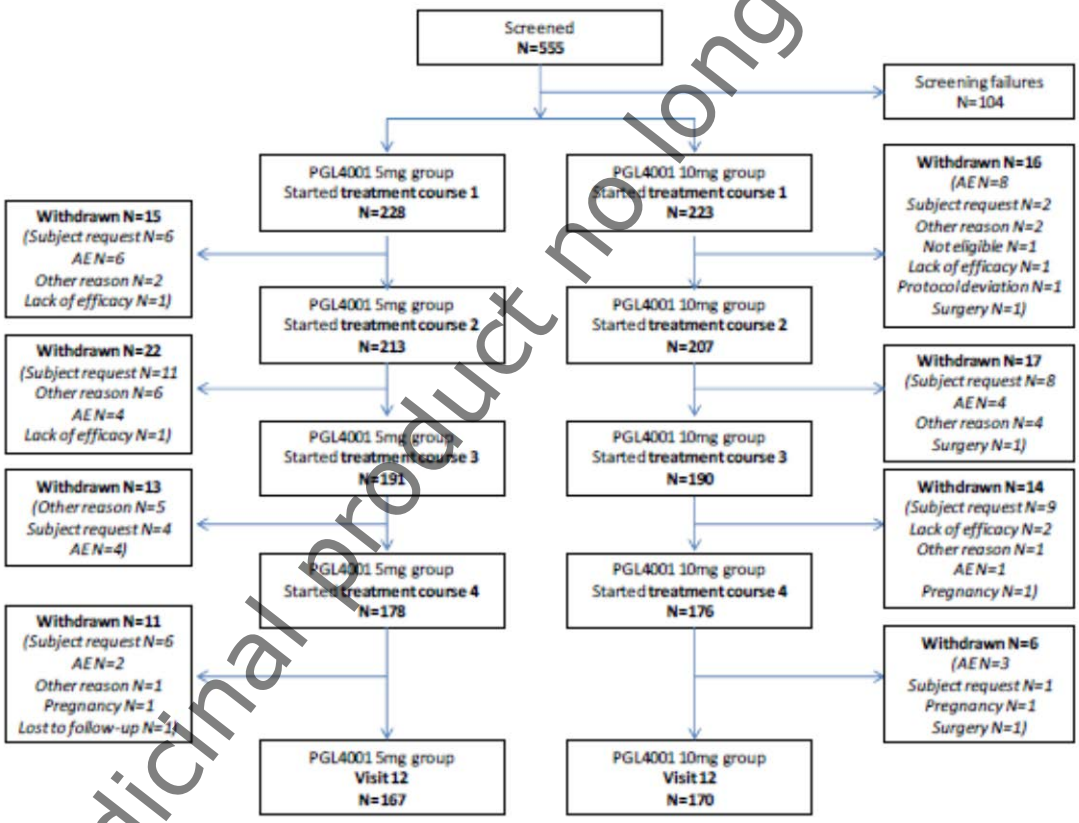

Figure 2: Disposition of subjects (as randomised)

Table 2: Subject Disposition

Disposition/Reasons	Treatment Group as Randomised		
	PGL4001 5mg	PGL4001 10mg	Total
Screened			555
Screening Failures			104
Attended each visit			
Screening 1			555
Screening 2			522
Screening 3			498
Visit 2			451
Randomised at Visit 2	228 (100.0%)	223 (100.0%)	451 (100.0%)
Attended each visit			
Visit 3	219 (96.1%)	218 (97.8%)	437 (96.9%)
Visit 4	218 (95.6%)	213 (95.5%)	431 (95.6%)
Visit 5	218 (95.6%)	214 (96.0%)	432 (95.8%)
Visit 6	216 (94.7%)	209 (93.7%)	425 (94.2%)
Telephone Call a	211 (92.5%)	204 (91.5%)	415 (92.0%)
Visit 7	205 (89.9%)	202 (90.6%)	407 (90.2%)
Visit 8	194 (85.1%)	193 (86.5%)	387 (85.8%)
Telephone Call b	192 (84.2%)	190 (85.2%)	382 (84.7%)
Visit 9	181 (79.4%)	181 (81.2%)	362 (80.3%)
Telephone Call c	177 (77.6%)	176 (78.9%)	353 (78.3%)
Visit 10	171 (75.0%)	172 (77.1%)	343 (76.1%)
Visit 11	169 (74.1%)	168 (75.3%)	337 (74.7%)
Telephone Call d	167 (73.2%)	165 (74.0%)	332 (73.6%)
Visit 12	167 (73.2%)	170 (76.2%)	337 (74.7%)
Received study medication			
Treatment Course 1	228 (100.0%)	223 (100.0%)	451 (100.0%)
Treatment Course 2	213 (93.4%)	207 (92.8%)	420 (93.1%)
Treatment Course 3	191 (83.8%)	190 (85.2%)	381 (84.5%)
Treatment Course 4	178 (78.1%)	176 (78.9%)	354 (78.5%)
Discontinued at any time*	61 (26.8%)	53 (23.8%)	114 (25.3%)
Discontinuation Reason:			
Not Eligible	0	1 (0.4%)	1 (0.2%)
Lack of Efficacy	2 (0.9%)	3 (1.3%)	5 (1.1%)
Adverse Event	16 (7.0%)	16 (7.2%)	32 (7.1%)
Adverse Event (Study Medication Related)	9 (3.9%)	13 (5.8%)	22 (4.9%)
Adverse Event (Unrelated to Study Medication)	7 (3.1%)	3 (1.3%)	10 (2.2%)
Subject Request	27 (11.8%)	20 (9.0%)	47 (10.4%)
Protocol Deviation	0	1 (0.4%)	1 (0.2%)
Lost to Follow-up	1 (0.4%)	0	1 (0.2%)
Surgery or Procedure for Fibroids	0	3 (1.3%)	3 (0.7%)
Pregnancy	1 (0.4%)	2 (0.9%)	3 (0.7%)
Other Reason	14 (6.1%)	7 (3.1%)	21 (4.7%)

Note: Denominator of percentage is the number of randomised subjects.
*Discontinued the study at any time: Fishers Exact Test p = 0.516.
Source: Table 14.1.1

Recruitment

The study was initiated the 26 June 2012 and completed the 19 December 2014.

Conduct of the study

Five major protocol deviations were reported. Two patients, both from the PGL4001 5 mg group, had major protocol deviations associated with compliance (one subject had 76.4% compliance during treatment course 1 and the other subject had 63.6% compliance during course 2). Three additional major protocol deviations occurred in the PGL4001 10 mg group, 2 at randomisation and 1 incorrect treatment allocation.

Compliance data were available for 224 of the 230 subjects in the 5 mg group and for 218 of the 221 subjects in the 10 mg group. The mean regimen compliance for subjects from the PGL4001 5 mg group was 99.3%, and the mean protocol compliance was 94.9%, reflecting the early termination of some subjects. For the 10 mg group, the mean regimen compliance was 99.4%, and the mean protocol compliance was 94.5%.

Baseline data

Table 3: Demographic Data

		Treatment Group as Randomised (Full Analysis Set 1)		Treatment Group as Received (Safety Set)		Full Analysis Set 1 / Safety Set
		PGL4001 5mg (N=228)	PGL4001 10mg (N=223)	PGL4001 5mg (N=230)	PGL4001 10mg (N=221)	Total (N=451)
Age (*)	N	228	223	230	221	451
	Mean	41.6	41.4	41.6	41.4	41.5
	SD	5.4	5.1	5.4	5.1	5.2
	Median	43.0	42.0	43.0	42.0	42.0
	Q1, Q3	38.0, 46.0	37.0, 46.0	38.0, 46.0	37.0, 46.0	38.0, 46.0
	Min, Max	19, 50	26, 50	19, 50	26, 50	19, 50
Ethnic Origin	White	211 (92.5%)	214 (96.0%)	213 (92.6%)	212 (95.9%)	425 (94.2%)
	Black	12 (5.3%)	8 (3.6%)	12 (5.2%)	8 (3.6%)	20 (4.4%)
	Asian	1 (0.4%)	0	1 (0.4%)	0	1 (0.2%)
	Hispanic	1 (0.4%)	0	1 (0.4%)	0	1 (0.2%)
	Other	2 (0.9%)	1 (0.4%)	2 (0.9%)	1 (0.5%)	3 (0.7%)
	Not reported	1 (0.4%)	0	1 (0.4%)	0	1 (0.2%)
Fertility Status	Not of Childbearing Potential	9 (3.9%)	15 (6.7%)	9 (3.9%)	15 (6.8%)	24 (5.3%)
	Of Childbearing Potential	219 (96.1%)	208 (93.3%)	221 (96.1%)	206 (93.2%)	427 (94.7%)
Weight (kg)	N	227	223	229	221	450
	Mean	69.15	69.99	69.17	69.98	69.57
	SD	12.72	12.76	12.67	12.81	12.73
	Median	67.00	67.00	67.00	67.00	67.00
	Q1, Q3	61.00, 75.10	60.00, 77.00	61.00, 75.00	60.00, 77.00	60.00, 76.00
	Min, Max	45.5, 116.7	47.0, 117.0	45.5, 116.7	47.0, 117.0	45.5, 117.0
Height (cm)	N	227	223	229	221	450
	Mean	165.5	166.5	165.5	166.4	166.0
	SD	6.0	5.8	6.1	5.7	5.9
	Median	165.0	166.0	165.0	166.0	166.0
	Q1, Q3	162.0, 170.0	163.0, 170.0	162.0, 170.0	163.0, 170.0	162.0, 170.0
	Min, Max	147, 184	150, 181	147, 184	150, 181	147, 184
Body Mass Index (kg/m^2)	N	227	223	229	221	450
	Mean	25.20	25.26	25.20	25.27	25.23
	SD	4.10	4.49	4.10	4.49	4.29
	Median	24.44	24.22	24.44	24.22	24.39
	Q1, Q3	22.31, 27.64	21.88, 28.23	22.31, 27.64	21.88, 28.13	22.04, 27.76
	Min, Max	18.0, 38.1	17.9, 39.5	18.0, 38.1	17.9, 39.5	17.9, 39.5

(*) Age at last birthday in whole years, using the date of informed consent.

All treated patients (451) had a diagnosis of uterine leiomyoma. Subjects from the PGL4001 5 mg and 10 mg groups had a similar medical and surgical history.

All subjects had very severe uterine bleeding with a mean (median) PBAC at screening of 302 (220) (range 33 to 2370). Overall, mean total fibroid volume was 84.6 cm^3 (ranging from 3.0 to 826 cm^3) and mean uterine volume was 227.3 cm^3 (ranging from 31.6 to 1286.0 cm^3). The uterine volume was comparable in the two treatment groups with an overall mean (median) of 227.3 (175.7) cm^3.

At screening, mean Hb was 12.27 g/dL and mean Hct was 39.8%. At baseline, 37.4% of the subjects were anaemic (Hb≤12 g/dL), and 10.6% of subjects had moderate to severe anaemia (Hb ≤ 10.2 g/dL).

Subjects in the PGL4001 5 mg and 10 mg groups had similar baseline conditions.

Concomitant medications were taken by a total of 245 (54.3%) of all subjects from the start of treatment course 1 until visit 12 of the study (Safety Set); 131 (57.0%) subjects from the PGL4001 5 mg group and 114 (51.6%) subjects from the PGL4001 10 mg group.

The most frequently taken medications were anti-inflammatory/anti-rheumatic products, taken by 19.7% of subjects (most commonly ibuprofen taken by 15.1% of subjects), analgesics and antipyretics, taken by 19.5% of subjects (most commonly paracetamol taken by 15.7% subjects), and iron products taken by 8.4% of all subjects.

At the start of this study, surgery was not planned for the majority of subjects (410 subjects, 90.9%), whereas in Studies PGL07-021 and PGL07-022 surgery was planned for all subjects enrolled, and in Study PGL09-026 it was planned for 44.3% of subjects. During the study, 435 (96.5%) subjects in the FAS 1 did not have surgery performed; surgery was performed on 16 (3.5%) subjects (7 [3.1%] and 9 [4.0%] in the PGL4001 5 mg and PGL4001 10 mg groups, respectively); for 13 of these surgery was not planned at the start of the study. The decision drivers for the 16 subjects that had surgery performed were reported as 'mainly Investigator recommendation' for 7 subjects, 'mainly driven by subject request' for 6 subjects (FAS 1), and 'equal influence' for 3 subjects. The main reason for surgery was reported as 'insufficient efficacy of treatment' for 6 subjects, 'poor tolerability to the treatment' for 1 subject and 'other' for 9 subjects. The 'other' main reasons for surgery were 'not compliant and frequent spotting', 'progression of strong pelvic pain – pelvic and ovarian endometriosis', 'patient wanted surgery', 'a myoma in status nascendi', 'ovarian cyst', 'the treatment made the myoma nodule smaller and it was a partial myoma in status nascendi with signs of infection', 'emergency partial expulsion of myoma', 'endometrial adenocarcinoma' and 'severe pelvic pain, necrosis of myoma node'.

Numbers analysed

Table 4: Analysis Sets

Analysis Set	Treatment Group		
	PGL4001 5 mg	PGL4001 10 mg	Total
Full Analysis Set 1 (1)	228	223	451
Full Analysis Set 2 (1)	213	207	420
Full Analysis Set 3 (1)	191	190	381
Full Analysis Set 4 (1)	178	176	354
Safety Set (2)	230	221	451
Per Protocol Set 1 (1)	219	212	431
Per Protocol Set 2 (1)	208	200	408
Per Protocol Set 3 (1)	188	187	375
Per Protocol Set 4 (1)	176	171	347
Not Treated			104

(1) Treatment group as randomised.
(2) Treatment group as received.
Note: 'Not Treated' includes all subjects who have had at least one screening assessment conducted but who have not subsequently received trial medication.
Source: Table 14.1.2

Outcomes and estimation

Primary efficacy endpoint

Percentage of subjects in amenorrhoea at the end of both treatment courses 1 and 2 (Part I)

A total of 384 subjects in the FAS 1 had an amenorrhoea assessment at the end of both treatment courses 1 and 2.

Table 5: Analysis of patients in amenorrhoea at the end of both treatment courses 1 and 2 (Full Analysis Set 1)

Subjects in Amenorrhoea	Treatment Group		
	PGL4001 5mg (N=228)	PGL4001 10mg (N=223)	Total (N=451)
Non-missing amenorrhoea assessment for Treatment Courses 1 and 2	197	187	384
Yes	122 (61.9%)	136 (72.7%)	258 (67.2%)
No	75 (38.1%)	51 (27.3%)	126 (32.8%)
Difference (PGL4001 10mg - PGL4001 5mg)		10.8%	
95% Confidence Interval (1)		1.5%, 20.1%	
p-value (2)		0.032	

Note: Amenorrhoea is defined as no more than one day of spotting within a 35 day interval. The denominator of percentage is the number of subjects with a non-missing amenorrhoea assessment for both treatment courses 1 and 2.
(1) Calculated using the Newcombe-Wilson score method.
(2) Analysed via a continuity-adjusted Chi-Squared Test.

Different sensitivity analyses were performed, for instance by imputing missing amenorrhoea assessments at the end of treatment courses 1 and/or 2 as a failure (not in amenorrhoea) or as a success (in amenorrhoea).

For sensitivity analysis 1, the number (percentage) of subjects in amenorrhoea at the end of both treatment courses 1 and 2 was 122 (53.5%) of 228 subjects and 136 (61.0%) of 223 subjects for the PGL4001 5 mg and PGL4001 10 mg groups, respectively. The difference was 7.5% (95% CI: -1.6% to 16.6%, p-value: 0.131).

For sensitivity analysis 2, missing amenorrhoea assessments at the end of treatment courses 1 and/or 2 were imputed as a success (in amenorrhoea). The corresponding number (percentage) of subjects in amenorrhoea for this sensitivity analysis was 145 (63.6%) and 168 (75.3%) for the 5 mg and 10 mg groups, respectively. The difference was 11.7% (95% CI: 3.3% to 20.2%, p-value: 0.009).

Analyses were also performed on the FAS 2 and PP Set 2, yielding fairly similar results as above.

Percentage of subjects in amenorrhoea at the end of all four treatment courses (Part II)

A total of 207 subjects in the FAS 1 had an amenorrhoea assessment at the end of all four treatment courses.

Table 6: Analysis of patients in amenorrhoea at the end of all four treatment courses (Full Analysis Set 1)

Subjects in Amenorrhoea	Treatment Group		
	PGL4001 5 mg (N=228)	PGL4001 10 mg (N=223)	Total (N=451)
Non-missing amenorrhoea assessment for all four treatment courses	195	185	380
Yes	95 (48.7%)	112 (60.5%)	207 (54.5%)
No	100 (51.3%)	73 (39.5%)	173 (45.5%)
Difference (PGL4001 10mg - PGL4001 5mg)		11.8%	
95% Confidence Interval (1)		1.9%, 21.8%	
p-value (2)		0.027	

Note: Amenorrhoea is defined as no more than one day of spotting within a 35 day interval. The denominator of percentage is the number of subjects with a non-missing amenorrhoea assessment for all four treatment courses.
(1) Calculated using the Newcombe-Wilson score method.
(2) Analysed via a continuity-adjusted chi-squared test.
Source: Table 14.2.2.1

A number of sensitivity analyses were conducted using the FAS 1 to investigate the effect of different assumptions when handling missing amenorrhoea information, with the corresponding results as follows:

For sensitivity analysis 1, missing amenorrhoea assessments at the end of treatment courses 1, 2, 3 and/or 4 were imputed as a failure (not in amenorrhoea). The number (percentage) of subjects in amenorrhoea at the end of all four treatment courses was 95 (41.7%) and 112 (50.2%) for the PGL4001 5 mg and PGL4001 10 mg groups, respectively. The difference was 8.6% (95% CI: -0.6% to 17.7%, p-value: 0.084).

For sensitivity analysis 2, missing amenorrhoea assessments at the end of treatment courses 1, 2, 3 and/or 4 were imputed as a success (in amenorrhoea). The number (percentage) of subjects in amenorrhoea at the end of all four treatment courses for this sensitivity analysis was 112 (49.1%) and 136 (61.0%) for the PGL4001 5 mg and PGL4001 10 mg groups, respectively. The difference was 11.9% (95% CI: of 2.7% to 21.0%, p-value: 0.015).

Sensitivity analysis 3 (up to 5 consecutive missing days were imputed prior to assessing amenorrhoea at the end of each treatment course) and sensitivity analysis 4 (only observed uterine bleeding data used in the assessment of amenorrhoea) provided similar differences between the 2 treatment groups compared to those of the primary analysis (differences: 11.7% and 10.4%, p-values: 0.024 and 0.208, respectively).

Secondary efficacy endpoints, including results from Study PGL09-027

A summary of efficacy results comparing the efficacy of ulipristal acetate at the end of different treatment courses both for studies PGL09-027 and PGL11-006 are presented below.

Table 7: Results of key efficacy endpoints in the long-term studies at the end of treatment courses 1 and 2, at the end of 1, 2, 3 and 4 treatment courses and at the end of treatment course 2 and 4 (Studies PGL09-027, ITT population and PGL11-006, FAS 1 population)

Parameter	Treatment course	Study PGL09-027	Study PGL11-006	
		10 mg/day ulipristal acetate N = 132	5 mg/day ulipristal acetate N = 228	10 mg/day ulipristal acetate N = 223
Subjects in **amenorrhoea at end of treatment course**, n (%) [95% CI]	**1 and 2**	n=131	n=197	n=187
		100 (76.3%) [68.4%, 82.8%]	122 (61.9%)	136 (72.7%)
Subjects in **amenorrhoea at end of treatment course**, n (%) [95% CI]	**1, 2, 3 and 4**	n=107	n=195	n=185
		77 (72.0%) [62.8%, 79.6%]	95 (48.7%)	112 (60.5%)
Subjects in **amenorrhoea at end of treatment course**	**After course 2**	n=131	n = 205	n = 197
		116 (88.5%)	152 (74.1%)	162 (82.2%)
	After course 4	n=107	n=227	n=220
		96 (89.7%)	158 (69.6%)	164 (74.5%)
Subjects with spotting / no bleeding **at end of treatment course**	**After course 2**	n=131	n=202	n=196
		123 (93.9%)	165 (81.7%)	171 (87.2%)
	After course 4	n=107	n=227	n=220
		100 (93.5%)	167 (73.6%)	168 (76.4%)
Subjects with **controlled bleeding**	**After course 2**	-	n=199	n=191
			175 (87.9%)	168 (88.0%)
	After course 4	-	n=202	n=192
			148 (73.3%)	144 (75.0%)
PBAC Post-treatment Median Change from Baseline	**After course 2**	n=123	n=152	n=146
		-150	-95	-109.5
	After course 4	n=89	n=140	n=138
		-120	-118	-121
Median change in **myoma volume** from baseline (3 largest myoma)	**After course 2**	n=119	n=198	n=200
		-63.2%	-54.1%	-58.0%
	After course 4	n=96	n=166	n=170
		-72.1%	-71.8%	-72.7%
n (%) with **myoma volume** reduction ≥25%	**After course 2**	95 (79.8%)	159 (80.3%)	156(83.0%)
	After course 4	79 (82.3%)	135 (81.3%)	150 (88.2%)
Median change in **uterine volume** from baseline	**After course 2**	n=121	n=205	n=203
		-32.3	-23.6%	-25.5%
	After course 4	n=96	n=170	n=171
		-40.24	-25.1%	-30.7%
n (%) with **uterine volume** reduction ≥25%	**After course 2**	73 (60.3%)	98 (47.8%)	103 (50.7%)
	After course 4	64 (66.7%)	85 (50.0%)	97 (56.7%)

n = number of subjects contributing to the endpoint

Of note, a small number of data updates were undertaken since the Part I database lock, which lead to very minor differences in data for treatment course 1 and 2 compared to those provided in the CSR Part I; all the conclusions of the CSR Part I remain entirely valid.

Source: Table 2.7.3- 58, PGL09-027 CSR Tables: 14.2.1.1.1, 14.2.2.1, 14.2.2.3, 14.2.6.1, 14.2.6.2, 14.2.9.2.1, 14.3.12.1, and PGL11-006 CSR Tables: 14.2.1.1, 14.2.2.1, 14.2.3.1, 14.2.11.1, 14.2.19.1, 14.2.21.1, 14.2.22.1, 14.2.24.1, 14.2.33 and 2.7.3 Appendix- Table 8.

Amenorrhoea at the end of each treatment course

A more detailed summary of subjects in amenorrhoea at the end of each treatment course and time to amenorrhoea is shown in Table 7 and Figure 3 below.

Table 8: Summary of subjects in amenorrhoea at the end of ulipristal acetate treatment course 1, 2, 3 and 4 (FAS 1 population) (Study PGL11-006)

Treatment Course			Treatment Group		
			PGL4001 5 mg (N=228)	PGL4001 10 mg (N=223)	Total (N=451)
1	Non-missing amenorrhoea assessment		216	207	423
	Subjects in Amenorrhoea	Yes	155 (71.8%)	171 (82.6%)	326 (77.1%)
		No	61 (28.2%)	36 (17.4%)	97 (22.9%)
		Difference (PGL4001 10mg - PGL4001 5mg)		10.8%	
		95% CI (1)		2.9%, 18.8%	
		p-value (2)		0.011	
	Time to Amenorrhoea (Days)	N	155	171	326
		Mean	10.8	8.3	9.5
		SD	14.0	10.8	12.5
		Median	5.0	4.0	4.0
		Q1, Q3	2.0, 9.0	2.0, 7.0	2.0, 8.0
		Min, Max	0, 49	0, 48	0, 49
2	Non-missing amenorrhoea assessment		205	197	402
	Subjects in Amenorrhoea	Yes	152 (74.1%)	162 (82.2%)	314 (78.1%)
		No	53 (25.9%)	35 (17.8%)	88 (21.9%)
		Difference (PGL4001 10mg - PGL4001 5mg)		8.1%	
		95% CI (1)		0.1%, 16.1%	
		p-value (2)		0.066	
	Time to Amenorrhoea (Days)	N	149	161	310
		Mean	10.5	9.0	9.7
		SD	12.3	10.2	11.3
		Median	5.0	6.0	5.0
		Q1, Q3	4.0, 9.0	4.0, 8.0	4.0, 8.0
		Min, Max	0, 47	0, 48	0, 48
3	Non-missing amenorrhoea assessment		225	221	446
	Subjects in Amenorrhoea	Yes	165 (73.3%)	173 (78.3%)	338 (75.8%)
		No	60 (26.7%)	48 (21.7%)	108 (24.2%)
		Difference (PGL4001 10mg - PGL4001 5mg)		4.9%	
		95% CI (1)		-3.0%, 12.9%	
		p-value (2)		0.267	
	Time to Amenorrhoea (Days)	N	161	166	327
		Mean	15.8	15.5	15.7
		SD	23.2	23.5	23.3
		Median	6.0	6.0	6.0
		Q1, Q3	4.0, 10.0	4.0, 9.0	4.0, 10.0
		Min, Max	0, 86	0, 116	0, 116

Treatment Course			Treatment Group		
			PGL4001 5 mg (N=228)	PGL4001 10 mg (N=223)	Total (N=451)
4	Non-missing amenorrhoea assessment		227	220	447
	Subjects in Amenorrhoea	Yes	158 (69.6%)	164 (74.5%)	322 (72.0%)
		No	69 (30.4%)	56 (25.5%)	125 (28.0%)
		Difference (PGL4001 10mg - PGL4001 5mg)		4.9%	
		95% CI (1)		-3.4%, 13.2%	
		p-value (2)		0.290	
	Time to Amenorrhoea (Days)	N	154	155	309
		Mean	16.6	16.2	16.4
		SD	24.9	24.7	24.8
		Median	5.0	5.0	5.0
		Q1, Q3	4.0, 9.0	4.0, 9.0	4.0, 9.0
		Min, Max	0, 88	1, 95	0, 95

Note: Amenorrhoea is defined as the first day for which there is no bleeding for longer than 35 days, assessed using the subject diary data from the date of first dose of PGL4001 (which was to be within the first four days of the start of menstruation for treatment course 1 and within the first two days of the start of menstruation for treatment courses 2, 3 and 4). One day of spotting in any 35 day interval is accepted. The denominator of percentage is the number of subjects with a non-missing amenorrhoea assessment within each treatment course.
(1) CI = Confidence interval, calculated using the Newcombe-Wilson score method.
(2) Analysed via a continuity-adjusted chi-squared test.
Source: Table 14.2.3.1

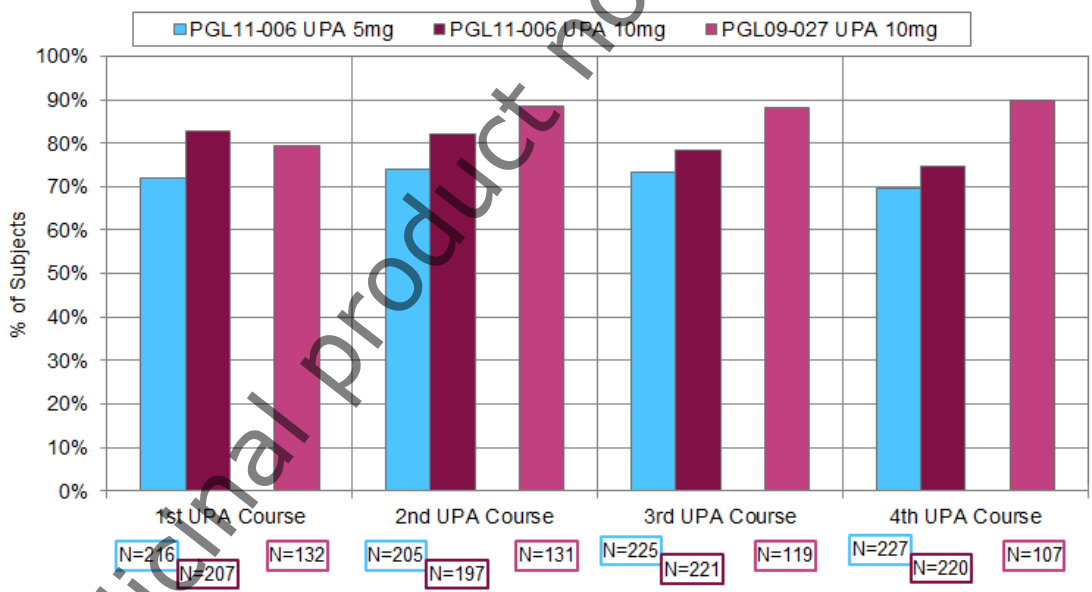

Figure 3: Subjects in Amenorrhea at the end of each treatment course (PGL11-006 Part 1: Full Analysis Set 1, PGL09-027: ITT Set)

Controlled bleeding

Controlled bleeding was defined as no episodes of heavy bleeding and a maximum of 8 days of bleeding over 56 days, i.e. 2 months.

Table 9: Subjects with controlled bleeding in the last 56 days of both treatment courses 1 and 2 (FAS 1 population) (Study PGL11-006 Part I)

Subjects with Controlled Bleeding in the last 56 days of Treatment	Treatment Group		
	Ulipristal acetate		Total (N=451)
	5 mg/day (N=228)	10 mg/day (N=223)	
Non-missing controlled bleeding assessment in the last 56 days of Treatment Courses 1 and 2	185	172	357
Yes	150 (81.1%)	148 (86.0%)	298 (83.5%)
No	35 (18.9%)	24 (14.0%)	59 (16.5%)
Difference (10mg/day - 5mg/day)		5.0%	
95% CI [a]		-2.7%, 12.6%	
p-value [b]		0.263	

Note: Controlled bleeding is defined as no episodes of heavy bleeding and a maximum of 8 days bleeding (not including days of spotting) during the last 56 days of a treatment course. The denominator of percentage is the number of subjects with a non-missing controlled bleeding assessment for both treatment courses 1 and 2.
a CI calculated using the Newcombe-Wilson score method.
b Analysed via a continuity-adjusted Chi-Squared Test.

CI = confidence interval, FAS = full analysis set.

Table 10: Analysis of subjects with controlled bleeding in the last 56 days of all four treatment courses (Full analysis set 1)

Subjects with Controlled Bleeding in the last 56 days of Treatment	Treatment Group		
	PGL4001 5mg (N=228)	PGL4001 10mg (N=223)	Total (N=451)
Non-missing controlled bleeding assessment in the last 56 days of all four treatment courses	158	146	304
Yes	106 (67.1%)	105 (71.9%)	211 (69.4%)
No	52 (32.9%)	41 (28.1%)	93 (30.6%)
Difference (PGL4001 10mg - PGL4001 5mg)		4.8%	
95% Confidence Interval (1)		-5.5%, 15.2%	
p-value (2)		0.430	

Note: Controlled bleeding is defined as no episodes of heavy bleeding and a maximum of 8 days bleeding (not including days of spotting) during the last 56 days of a treatment course. The denominator of percentage is the number of subjects with a non-missing controlled bleeding assessment for all four treatment courses.
(1) CI = Confidence interval, calculated using the Newcombe-Wilson score method.
(2) Analysed via a continuity-adjusted chi-squared test.

Median time to amenorrhoea

Median time to amenorrhoea was 8 days and 5 days in the 5 mg/day group and 10 mg/day group, respectively, for treatment course 1. Similarly, median time to amenorrhoea was 7 days and 6 days in the 5 mg/day group and 10 mg/day group, respectively, for treatment course 2. Median time to amenorrhoea was 6 days for both the PGL4001 5 mg and PGL4001 10 mg group for treatment course 3 as well as for treatment course 4.

Table 11: Kaplan-Meier estimates of subjects in amenorrhoea at the end of each treatment course (FAS 1 population) (Study PGL11-006)

Treatment Course			Treatment Group		
			PGL4001 5 mg (N=228)	PGL4001 10 mg (N=223)	Total (N=451)
1	Non-missing amenorrhoea assessment		228	223	451
	Subjects in Amenorrhoea		155 (68.0%)	171 (76.7%)	326 (72.3%)
	Censored Subjects		73 (32.0%)	52 (23.3%)	125 (27.7%)
	Probability of Amenorrhoea	Probability	0.698	0.778	0.738
		95% CI	0.636, 0.757	0.721, 0.831	0.696, 0.778
	Time to Amenorrhoea (Days)	N	228	223	451
		Q1	3	3	3
		Median	8	5	6
		Q3*		36	
2	Non-missing amenorrhoea assessment		212	205	417
	Subjects in Amenorrhoea		151 (71.2%)	161 (78.5%)	312 (74.8%)
	Censored Subjects		61 (28.8%)	44 (21.5%)	105 (25.2%)
	Probability of Amenorrhoea	Probability	0.715	0.800	0.757
		95% CI	0.652, 0.775	0.742, 0.852	0.714, 0.797
	Time to Amenorrhoea (Days)	N	210	204	414
		Q1	4	4	4
		Median	7	6	7
		Q3*		35	47
3	Non-missing amenorrhoea assessment		191	190	381
	Subjects in Amenorrhoea		159 (83.2%)	169 (88.9%)	328 (86.1%)
	Censored Subjects		32 (16.8%)	21 (11.1%)	53 (13.9%)
	Probability of Amenorrhoea	Probability	0.934	0.915	0.936
		95% CI	0.859, 0.977	0.860, 0.952	0.886, 0.969
	Time to Amenorrhoea (Days)	N	191	187	378
		Q1	4	4	4
		Median	6	6	6
		Q3	47	34	40
4	Non-missing amenorrhoea assessment		178	176	354
	Subjects in Amenorrhoea		154 (86.5%)	156 (88.6%)	310 (87.6%)
	Censored Subjects		24 (13.5%)	20 (11.4%)	44 (12.4%)
	Probability of Amenorrhoea	Probability	0.980	0.952	0.983
		95% CI	0.915, 0.998	0.891, 0.984	0.934, 0.998
	Time to Amenorrhoea (Days)	N	178	175	353
		Q1	4	4	4
		Median	6	6	6
		Q3	53	37	42

Note: Amenorrhoea is defined as the first day for which there is no bleeding for longer than 35 days, assessed using the subject diary data from date of first dose of study medication (which was to be within the first 4 days of the start of menstruation for treatment course 1 and on the first or second day of menstruation for treatment courses 2, 3 and 4) to the end of study medication within each treatment course. One day of spotting in any 35 day interval is accepted. Subjects are considered censored if they have an interval of 35 days or less up to the end of the treatment course for which no more than one day of spotting was observed (censored at the first day of this interval) or who record bleeding or heavy bleeding or who have a missing bleeding record at the end of the treatment course (censored at the end of the treatment course). The denominator of percentage is the number of subjects with a non-missing amenorrhoea assessment within each treatment course. CI = Confidence interval.
* Upper quartile (Q3) could not be calculated for PGL4001 5 mg, treatment course 1 and treatment course 2

Source: Table 14.2.18.1

PBAC during the off-treatment periods

The mean (median) PBAC scores associated with return of menstruation decreased after each subsequent treatment course. The extent of reduction in the ulipristal acetate + Placebo group in Study PGL09-027 was similar to that observed in the two treatment groups in Study PGL11-006. In Study PGL09-027, NETA had an additional positive impact on the reduction of menstrual bleeding.

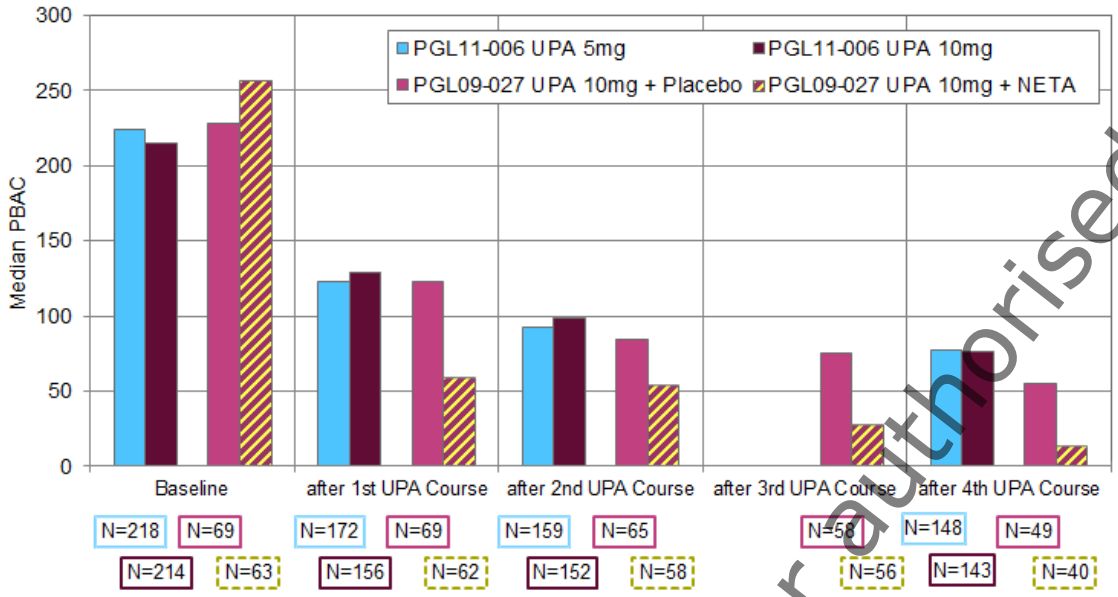

Figure 4: Median PBAC Assessment on Intensity of Menstrual Bleeding at Baseline and of First Menstruation after end of UPA Treatment Course (PGL11-006: Full Analysis Set 1, PGL09-027: Safety Set)

Fibroid size

In the FAS 1 population, the mean (median) total volume at screening 3 was 76.87 cm^3 (42.61 cm^3) and 92.32 cm^3 (43.57 cm^3) in the 5 mg/day group and 10 mg/day group, respectively.

In terms of fibroid volume reduction, the total volume of the 3 largest fibroids identified at screening was shown to decrease following the first treatment course, and to further decrease after each treatment course, with no statistically significant differences identified between the two treatment groups. The mean (median) total volume of the 3 largest myomas at end of treatment course 2 (Visit 7) had been 44.59 cm^3 (19.23 cm^3) and 57.10 cm^3 (19.83 cm^3) for the PGL4001 5 mg and PGL4001 10 mg groups, respectively. By the end of treatment course 4 (Visit 10) the mean (median) volume of the 3 largest myomas was decreased to 41.23 cm^3 (13.27 cm^3) and 39.02 cm^3 (13.68 cm^3) for the PGL4001 5 mg and PGL4001 10 mg groups, respectively. The mean (median) percent change from baseline (screening 3) to visit 10 was -37.09% (-71.83%) and -57.80% (-72.73%) in the PGL4001 5 mg and PGL4001 10 mg groups, respectively.

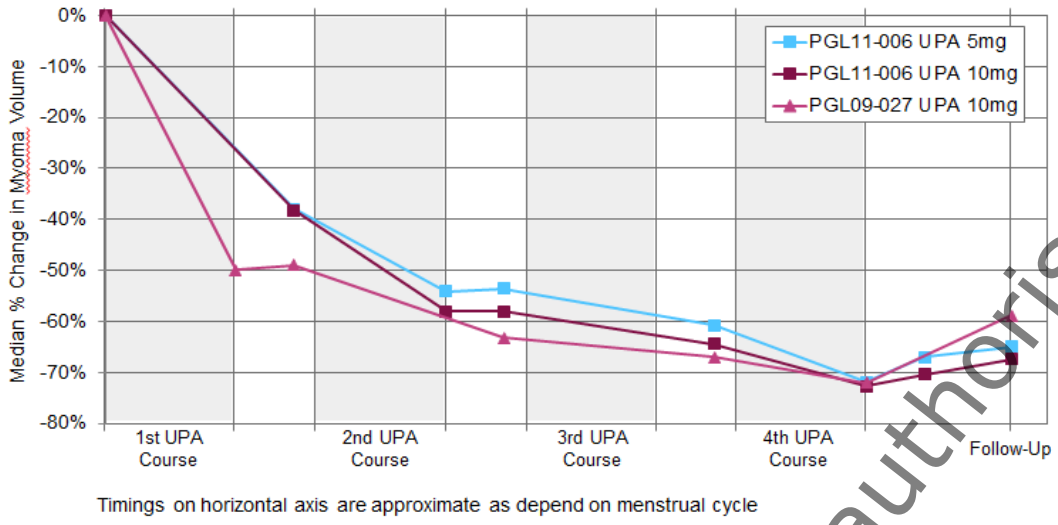

Figure 5: Median Percentage Change from Screening in Myoma Volume versus UPA Treatment Course (PGL11-006: Full Analysis Set 1, PGL09-027: ITT Set)

The percentages of subjects with a reduction in myomas size of ≥25% and ≥50% at different time points are shown in Table 12.

Table 12: Summary of the total volume of the three largest myomas with reduction from baseline ≥25% and 50% (FAS 1 population) (Study PGL11-006)

Visit	Myoma Volume Reduction from Baseline	Treatment Group PGL4001 5mg (N=228)	PGL4001 10mg (N=223)	Total (N=451)
Visit 6	Non-missing	207	206	413
	Volume Reduction ≥25%	129 (62.3%)	137 (66.5%)	266 (64.4%)
	Volume Reduction ≥50%	77 (37.2%)	71 (34.5%)	148 (35.8%)
Visit 7	Non-missing	198	200	398
	Volume Reduction ≥25%	159 (80.3%)	166 (83.0%)	325 (81.7%)
	Volume Reduction ≥50%	116 (58.6%)	115 (57.5%)	231 (58.0%)
Visit 8	Non-missing	189	193	382
	Volume Reduction ≥25%	140 (74.1%)	153 (79.3%)	293 (76.7%)
	Volume Reduction ≥50%	101 (53.4%)	117 (60.6%)	218 (57.1%)
Visit 9	Non-missing	173	177	350
	Volume Reduction ≥25%	130 (75.1%)	147 (83.1%)	277 (79.1%)
	Volume Reduction ≥50%	107 (61.8%)	120 (67.8%)	227 (64.9%)
Visit 10	Non-missing	166	170	336
	Volume Reduction ≥25%	135 (81.3%)	150 (88.2%)	285 (84.8%)
	Volume Reduction ≥50%	111 (66.9%)	124 (72.9%)	235 (69.9%)
Visit 11	Non-missing	160	159	319
	Volume Reduction ≥25%	125 (78.1%)	128 (80.5%)	253 (79.3%)
	Volume Reduction ≥50%	102 (63.8%)	113 (71.1%)	215 (67.4%)
Visit 12	Non-missing	158	160	318
	Volume Reduction ≥25%	121 (76.6%)	133 (83.1%)	254 (79.9%)
	Volume Reduction ≥50%	102 (64.6%)	113 (70.6%)	215 (67.6%)

Note: Denominator of percentage is the number of subjects with a non-missing myoma volume reduction at each visit.
Source: Table 14.2.21.1

Uterine volume reduction

Similar to the fibroid size, the volume of the uterus as measured by ultrasound decreased upon treatment with ulipristal acetate. The uterine volume decreased following each treatment course with no statistically significant differences between the two treatment groups at any visit.

The percentage of subjects with a reduction in uterine volume of ≥25% and ≥50% at different time points are shown in Table 13.

Table 13: Summary of uterine volume with reduction from baseline ≥25% and ≥50% (FAS 1 population) (Study PGL11-006)

Visit	Uterine Volume Reduction from Baseline	Treatment Group		
		PGL4001 5 mg (N=228)	PGL4001 10 mg (N=223)	Total (N=451)
Visit 6	Non-missing	214	211	425
	Volume Reduction ≥25%	63 (29.4%)	66 (31.3%)	129 (30.4%)
	Volume Reduction ≥50%	13 (6.1%)	13 (6.2%)	26 (6.1%)
Visit 7	Non-missing	205	203	408
	Volume Reduction ≥25%	98 (47.8%)	103 (50.7%)	201 (49.3%)
	Volume Reduction ≥50%	31 (15.1%)	37 (18.2%)	68 (16.7%)
Visit 8	Non-missing	194	196	390
	Volume Reduction ≥25%	90 (46.4%)	90 (45.9%)	180 (46.2%)
	Volume Reduction ≥50%	18 (9.3%)	31 (15.8%)	49 (12.6%)
Visit 9	Non-missing	182	182	364
	Volume Reduction ≥25%	74 (40.7%)	84 (46.2%)	158 (43.4%)
	Volume Reduction ≥50%	20 (11.0%)	26 (14.3%)	46 (12.6%)
Visit 10	Non-missing	170	171	341
	Volume Reduction ≥25%	85 (50.0%)	97 (56.7%)	182 (53.4%)
	Volume Reduction ≥50%	32 (18.8%)	44 (25.7%)	76 (22.3%)
Visit 11	Non-missing	168	165	333
	Volume Reduction ≥25%	74 (44.0%)	79 (47.9%)	153 (45.9%)
	Volume Reduction ≥50%	26 (15.5%)	38 (23.0%)	64 (19.2%)
Visit 12	Non-missing	167	170	337
	Volume Reduction ≥25%	69 (41.3%)	73 (42.9%)	142 (42.1%)
	Volume Reduction ≥50%	22 (13.2%)	36 (21.2%)	58 (17.2%)

Note: Denominator of percentage is the number of subjects with a non-missing uterine volume reduction at each visit.
Source: Table 14.2.24.1

Effect on Haemoglobin

In Study PGL11-006, 40% of subjects had Hb ≤12 g/dL at baseline, including 12% with more severe anaemia with equal distribution between the two treatment arms. After one treatment course, the percentage of subjects being anaemic decreased to 21% and 17% for subjects in the 5 mg and 10 mg group, respectively. The percentage of subjects with more severe anaemia was decreased to 3% and 4% for the 5 mg and 10 mg group respectively, with no difference between treatment groups.

Quality of Life assessments

The improvements in symptom severity and HRQoL total scores were similar in the two treatment groups and were partially maintained during the off-treatment interval between treatment course 1 and treatment course 2. During treatment, both treatment groups reached symptom severity and total HRQoL scores similar to those observed in healthy women.

In the total treatment group, the mean symptom severity score (UFS-QoL) at baseline was 48.73, with baseline scores being very similar in the two treatment groups.

Regarding the UFS-QoL, at the end of treatment course 1 compared to baseline, the mean (median) change from baseline was of -32.30 (-34.38) and -31.19 (-31.25) in the PGL4001 5 mg and PGL4001 10 mg treatment groups, respectively. At the end of treatment course 2 compared to baseline, the mean (median) change was of -27.89 (-28.13) and -27.28 (-28.13) in the PGL4001 5 mg and PGL4001 10 mg groups, respectively. At the end of treatment course 3, the mean (median) change from baseline was -29.48 (-28.13) and -29.40 (-31.25) in the PGL4001 5 mg and 10 mg groups, respectively. At the end of treatment course 4, the mean (median) change from baseline was -29.81 (-31.25) and -29.81 (-28.13) in the PGL4001 5 mg and 10 mg groups, respectively.

The pattern of improvement was similar for the HRQoL.

In the EQ-5D questionnaire, the most complaints at baseline and throughout the study were in the pain/discomfort and anxiety/depression dimensions.

Compared to baseline, at Visit 5, the percentage of subjects exhibiting moderate pain/discomfort was reduced in both treatment groups, from 44.4% to 22.3% in the 5 mg/day group and from 45.0% to 23.5% subjects in the 10 mg/day group. The percentage of subjects exhibiting extreme pain/discomfort decreased from 4.5% to none in the 5 mg/day group and from 6.8% to 0.9% in the 10 mg/day group. At Visit 7, the numbers (percentages) of subjects with moderate and extreme pain/discomfort in the two treatment groups were similar to those observed at Visit 5 (end of treatment).

Compared to baseline, at Visit 5 the percentage of subjects exhibiting moderate anxiety/depression was reduced in both treatment groups, from 29.9% to 16.7% in the 5 mg/day group and from 28.6% to 0.9% in the 10 mg/day group. Similarly, the percentage of subjects exhibiting extreme anxiety/depression decreased from 3.2% to 0.9% in the 5 mg/day group and from 3.6% to 0.9% in the 10 mg/day group. At Visit 7, the numbers (percentages) of subjects exhibiting moderate and extreme anxiety/depression in the two treatment groups were similar to those observed at Visit 5.

This improvement was maintained at visits 7 and 10 (end of treatment courses 2 and 4) through to end of study follow-up at visit 12.

Pain

Pain was assessed by VAS (over a recall period of 1 month) for both the FAS 1 population and a subgroup of subjects with severe pain at baseline (VAS score >40).

At the start of treatment course 1 (baseline) the mean pain VAS scores were 39.7 and 42.6 for the ulipristal acetate 5 mg/day and 10 mg/day groups, respectively.

For the FAS 1, at the end of treatment course 1, both treatment groups showed a similar improvement (decrease) from baseline with a mean (median) change of -26.2 (-24.5) in the PGL4001 5 mg group and -28.3 (-25.0) in the PGL4001 10 mg group. After the off-treatment interval and return of menstruation at the start of treatment course 2 (start of the second menstruation following the end of treatment course 1), there was still an improvement from baseline on average but less than seen at the end of treatment course 1, with mean (median) change from baseline of -7.3 (-3.0) and -14.7 (-8.0) in the PGL4001 5 mg and PGL4001 10 mg groups, respectively. At the end of treatment course 2, there was an average improvement compared to baseline with a mean (median) change from baseline of -22.3 (-23.0) and -25.6 (-24.0) in the PGL4001 5 mg and PGL4001 10 mg groups, respectively. The pattern of improvement from baseline continued over the next two treatment courses; at the end of treatment course 3, there was a mean (median) change from baseline of -26.1 (-20.5) and -28.2 (-24.5) in the PGL4001 5 mg and PGL4001 10 mg groups, respectively, and at the end of treatment course 4, there was a mean (median) change from baseline of -21.2 (-20.0) and -27.3 (-23.0) in the PGL4001 5 mg and PGL4001 10 mg groups, respectively. The decrease from baseline in pain VAS score at the start of each treatment course was slightly less than seen at the end of the treatment course. There was no evidence of a difference in the change from baseline in pain VAS between the two treatment groups.

The average pain VAS score continued to show an improvement (decrease) post-treatment; at visit 12 (end of study follow-up visit) the mean (median) change from baseline was -14.9 (-16.0) and -18.2 (-19.0) in the PGL4001 5 mg and PGL4001 10 mg groups, respectively.

Summary of main study

The following table summarises the efficacy results from the main study supporting the present application.

This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 14: Summary of Efficacy for trial PGL11-006

Title: A Phase III, multicentre, randomised, double-blind clinical study, investigating the efficacy and safety of repeated 12-week courses of daily 5 mg or 10 mg doses of PGL4001 for the long-term management of symptomatic uterine fibroids.			
Study identifier	**PGL11-006**		
Design	Multicentre, randomised, double-blind		
	Duration of main phase: Duration of run-in phase: Duration of extension phase:		The study includes 4 intermittent treatment courses, with 12 weeks (84 days) daily treatment with PGL4001 5 mg or 10 mg. Treatment courses were separated by a drug-free period, until start of the second menstruation following the end of the previous treatment course. Part I covers treatment courses 1 and 2 up to visit 8. Part II covers treatment courses 3 and 4 up to visit 12. not applicable not applicable
Hypothesis	Superiority		
Treatment groups	PGL4001 5 mg		PGL4001 5 mg + placebo of the PGL4001 10 mg tablet, 84 days per treatment course, (n=228)
	PGL4001 10 mg		PGL4001 10 mg + placebo of the PGL4001 5 mg tablet, 84 days per treatment course, (n=223)
Endpoints and definitions	Primary endpoint	Amenorrhoea	Percentage of subjects in amenorrhoea at the end of both treatment courses 1 and 2.(Part I) Percentage of subjects in amenorrhoea at the end of all four treatment courses (Part II)
	Secondary endpoints	Amenorrhoea Controlled bleeding	Percentage of subjects in amenorrhoea at the end of treatment course 1 and 2 (Part I) and course 3 and 4 (Part II), respectively, in the last 56 days, time to amenorrhoea, etc. Percentage of subjects with controlled bleeding in the last 56 days of treatment course 1 and 2 (Part I) and course 3 and 4 (Part II), respectively.

	Secondary endpoints	Myoma volume Uterine volume QoL Pain	Change from baseline to visits 6, 7 and 8 (Part I) and visits 9, 10, 11 and 12 (Part II) in the volume of the 3 largest myomas, measured by transvaginal US. Change from baseline to visits 6, 7 and 8 (Part I) and to visits 9, 10, 11 and 12 (Part II) in uterus volume, measured by transvaginal US. Change from baseline to end of treatment course 1 and 2 (Part I) and course 3 and 4 (Part II) in QoL, measured with UFS-QoL and EQ-5D Change from baseline to end of treatment course 1 and 2 (Part I) and to end of treatment course 3 and 4 (Part II) in pain, measured by VAS
Database lock	27 February 2014 (Part I) Final report Part I: 28 May 2014 Final report Part II: 12 March 2015		

Results and analysis

Analysis description	**Primary analysis**		
Analysis population and time point description	FAS 1 (all randomised subjects who received study medication at least once during course 1)		
	Part I		
Descriptive statistics and estimate variability	Treatment group	PGL4001 5 mg	PGL4001 10 mg
	Number of subjects	197	187
	Primary end-point: Subjects in amenorrhoea at end of two treatment courses	122 (61.9%)	136 (72.7%)
	Number of subjects	185	172
	Subjects with Controlled Bleeding in the Last 56 Days of the two Treatment Courses 1 and 2	150 (81.1%)	148 (86.0%)
	Number of subjects	228	223
	Change from Baseline in Volume of the Three Largest Myomas, Visit 8 (Ratio to baseline; LS mean)	0.432	0.363
Effect estimate per comparison	Primary endpoint: Amenorrhoea	Comparison groups	PGL4001 5 mg vs. 10 mg

		Difference (PGL4001 10mg - PGL4001 5mg)	10.8%
		95% Confidence Interval	1.5%, 20.1%
		P-value	0.032
	Secondary endpoint: Controlled bleeding	Comparison groups	PGL4001 5 mg vs. 10 mg
		Difference (PGL4001 10mg - PGL4001 5mg)	5.0%
		95% Confidence Interval	-2.7%, 12.6%
		P-value	0.263
	Secondary endpoint: Change from Baseline in Volume of the Three Largest Myomas, Visit 8	Comparison groups	PGL4001 5 mg vs. 10 mg
		Ratio (PGL4001 10mg/PGL4001 5mg)	0.840
		95% Confidence Interval	0.693, 1.019
		P-value	0.076

	Part II		
Descriptive statistics and estimate variability	Treatment group	PGL4001 5 mg	PGL4001 10 mg
	Number of subjects	195	185
	Primary end-point: Subjects in amenorrhoea at end of the four treatment courses	95 (48.7%)	112 (60.5%)
	Number of subjects	158	146
	Subjects with Controlled Bleeding in the Last 56 Days of the four Treatment Courses	106 (67.1%)	105 (71.9%)
	Number of subjects	228	223
	Change from Baseline in Volume of the Three Largest Myomas, Visit 12 (Ratio to baseline; LS mean)	0.328	0.286
Effect estimate per comparison	Primary endpoint: Amenorrhoea	Comparison groups	PGL4001 5 mg vs. 10 mg
		Difference (PGL4001 10mg - PGL4001 5mg)	11.8%
		95% Confidence Interval	1.9%, 21.8%
		P-value	0.027

	Secondary endpoint: Controlled bleeding	Comparison groups	PGL4001 5 mg vs. 10 mg
		Difference (PGL4001 10mg - PGL4001 5mg)	4.8%
		95% Confidence Interval	-5.5%, 15.2%
		P-value	0.430
	Secondary endpoint: Change from Baseline in Volume of the Three Largest Myomas, Visit 12	Comparison groups	PGL4001 5 mg vs. 10 mg
		Ratio (PGL4001 10mg/PGL4001 5mg)	0.872
		95% Confidence Interval	0.6669, 1.138
		P-value	0.314
Notes	None.		
Analysis description	All statistical hypothesis tests and CIs were two sided, using a 5% level of statistical significance. The primary efficacy endpoint was the percentage of subjects in amenorrhoea at the end of both treatment courses 1 and 2 (Part I) or all four courses (Part II), which was summarised by descriptive statistics for each treatment group and overall. The results obtained with the two doses of ulipristal acetate (5 mg and 10 mg) were compared using a continuity-adjusted chi-squared test. The confidence interval for the difference between PGL4001 5mg and PGL4001 10mg was also presented, using the Newcombe-Wilson score method. The secondary endpoints of percentage or proportions were analysed using the same method employed for the primary analysis.		

Analysis performed across trials (pooled analyses and meta-analysis)

No pooled analysis or meta-analysis have been performed by the applicant. However, indirect comparisons have been made between studies PGL09-027 and PGL11-006, as shown above.

2.5.2. Discussion on clinical efficacy

Design and conduct of clinical studies

Results from study PGL11-006 providing data for up to 4 treatment courses with ulipristal acetate were submitted in support of this variation application along with data for repeated treatment courses from the previously submitted study PGL09-026 and its extension PGL09-027. Study PGL11-006 was completed in two parts: Part I presented data after completion of treatment courses 1 and 2, up to visit 8 and Part II presented data after completion of all four treatment courses, up to visit 12.

The dose proposed for the new indication for long-term, intermittent use is the same as the approved dose for preoperative treatment, i.e. 5 mg per day. It was hypothesised that the 10 mg dose may have some advantages in term of efficacy over the 5 mg dose regimen for repeated intermittent administration. Hence, study PGL11-006 evaluated the efficacy and safety of ulipristal acetate 5 mg and 10 mg whereas study PGL09-026/027 only included the 10 mg dose.

The inclusion and exclusion criteria of study PGL11-006 were acceptable and largely in line with those used in previous studies with ulipristal acetate, except that the women included in this study were not required to be eligible for a surgical procedure for their myomas.

The design with intermittent treatment courses was used to allow menstrual shedding of the endometrium and a complete menstrual cycle to take place between each treatment course, with physiological progesterone influence on the endometrium.

No placebo or active control arms were included. A placebo arm was considered unethical in patients with heavy menstrual bleeding and an active comparator control was not available due to the long duration of the study. These arguments are endorsed.

The efficacy parameters chosen for this study are considered relevant, e.g. assessment of bleeding by PBAC, myoma volume, pain and quality of life. The primary endpoint was the percentage of patients who are in amenorrhoea at the end of both treatment courses 1 and 2 for Part I of the study and at the end of the 4 treatment courses for Part II of the study. Amenorrhoea is a rather strict endpoint, since it was defined as having no more than 1 day of spotting within a 35-day interval. For comparison with the pivotal phase 3 studies in the initial marketing authorisation for Esmya, the co-primary endpoints were percentage of patients with reduction in uterine bleeding defined as PBAC score <75 at end of treatment and change in total myoma volume assessed by MRI from screening to end of treatment in Study PGL07-21. In study PGL07-22, the primary endpoint was the percentage of subjects with reduction in uterine bleeding defined as PBAC score <75 at end of treatment.

The sample size calculation methods and the statistical methods are considered adequate for the study.

In studies with long period of diary data, the amount of missing data is always a concern. In the FAS 1 population, 63.0% subjects had sufficient uterine bleeding data to allow assessment of the primary endpoint using observed data only. Analysis on observed data only was presented as well as other sensitivity analyses handling early discontinuations. The analyses were pre-planned and adequate to address possible missing data scenarios.

Efficacy data and additional analyses

In total, 114 (25.3%) subjects, i.e. 61 (26.8%) subjects from the PGL4001 5 mg group and 53 (23.8%) subjects from the PGL4001 10 mg group, discontinued the study after the start of treatment course 1 up to the end of study follow-up visit (visit 12), equally distributed between the treatment groups. The most common reasons were subject's request and adverse events. Reasons for discontinuation did not show any distinct pattern. Some women discontinued since they had no return to menses within 90 days of the last dose and some due to lack of improvement.

All treated subjects had a diagnosis of uterine leiomyoma and all subjects had very severe uterine bleeding with a mean (median) PBAC at screening of 302 (220). The baseline demographic and disease characteristics were similar for the two treatment groups. The study population included was rather similar to that included in previous studies, i.e. predominantly white women, aged just above 40 years, with a BMI of approximately 25 and the majority were of child-bearing potential. The disease characteristics were also rather similar to previous phase 3 studies, although mean PBAC, fibroid volume and uterine volume were slightly lower in this study. Surgery was initially planned for less than 10% of the women and a small number of women (n=16, 3.5%) underwent surgery in the study.

For the primary efficacy endpoint, 62% of subjects were in amenorrhoea at the end of both treatment courses 1 and 2 in the 5 mg group compared to 73% subjects in the 10 mg group. Thus, there was a difference between the doses of about 10%. For comparison, 76% of the women in study PGL09-027 were in amenorrhea at the end of both treatment courses 1 and 2 and 72% had amenorrhea at the end of treatment courses 1, 2, 3 and 4.

The proportion of subjects in amenorrhoea at the end of treatment course 4 was somewhat lower compared to the end of course 2 for both doses. However, the proportions are still considered to be of clinical relevance and 73.3 % of the patients on the 5 mg dose had controlled bleeding (no episodes of heavy bleeding and a maximum of 8 days of bleeding over 56 days) after treatment course 4. At the end of all 4 treatment courses, in the 5 mg group, 49 % of the women were in amenorrhoea compared to 61 % subjects in the PGL4001 10 mg group (p= 0.027) for the FAS 1. This proportion may seem low. However, the proportions are considerably higher after each treatment course and of clear clinical relevance.

The mean (median) PBAC scores associated with return of menstruation decreased after each subsequent treatment course. Both fibroid volume and uterine volume decreased during the study. The total volume of the 3 largest myomas was shown to decrease following the second treatment course (-54 and -58% respectively for 5 mg and 10 mg), and to further decrease after each treatment course (about-72%). The reduction in volume was maintained thereafter until the end of study follow-up with no statistically significant differences seen between the two treatment groups at any visit in any of the analysis sets.

The uterine volume as measured by US was shown to decrease following the first treatment course, and to further decrease following each treatment course, with a maintained reduction in volume thereafter which was slightly reduced at the end of study follow-up. A similar response was seen for subjects from both the PGL4001 5 mg and 10 mg groups, with no statistically significant differences between the treatment groups.

The total volume of the 3 largest fibroids identified at screening was shown to decrease following the first treatment course, and to further decrease after each treatment course, with no statistically significant differences identified between the two treatment groups. The mean (median) percent change from baseline (screening 3) to visit 10 was -38% (-72%) and -58% (-73%) in the PGL4001 5 mg and PGL4001 10 mg groups, respectively.

By the end of treatment course 4, 81% and 88% had a ⩾25% myoma volume reduction in the PGL4001 5 mg and PGL4001 10 mg treatment groups, respectively.

Both doses of UPA showed improvement in quality of life measurements evaluated using the specific UFS-QoL symptom severity and HRQoL scales.

During the off-treatment interval, with resumption of menstruation the quality of life was slightly reduced compared to the end of each treatment course, but was still improved in comparison to baseline. No difference between the two treatment groups could be observed.

Overall, the efficacy results of Study PGL11-006 were in line with previously performed short-term and long-term Phase III studies. In this study, the 5 mg dose was included, whereas the previous long-term study PGL09-026 and its extension PGL09-027 only included data for the 10 mg dose. For several endpoints, the 10 mg dose was somewhat better than the 5 mg dose, however, for other endpoints (controlled bleeding, uterine and fibroid volume) there were no or only small differences. Due to the overall small differences, the choice of the 5 mg dose is deemed adequate.

2.5.3. Conclusions on the clinical efficacy

Final results of study PGL11-006 showed that 73.3 % of the patients on the 5 mg dose had controlled bleeding (no episodes of heavy bleeding and a maximum of 8 days of bleeding over 56 days) after treatment course 4 which is considered to be of clinical relevance. In addition, the proportions of patients in amenorrhoea after each treatment course are of clear clinical relevance supporting repeated intermittent treatment with ulipristal acetate.

Long term treatment has been studied up to 4 intermittent treatment courses. Additional data will be available from two studies (study PGL11-024 and study PGL14-001). The currently ongoing study PGL11-024 (the second extension of PGL09-026, i.e. following PGL09-027) will provide safety and efficacy data of up to 8 treatment courses, i.e. data on 4 additional treatment courses further to the data submitted in this variation (see RMP).

2.6. Clinical safety

Introduction

Clinical safety data for ulipristal acetate are available from 5 short-term completed Phase II and III studies (4 randomised, double-blind studies, 1 open-label study) and two long-term Phase III studies (1 completed open-label study PGL09-027, and 1 ongoing, randomised, double-blind study PGL11-006 for which Part I is completed). All studies were carried out in the target population. Additional safety data are available from 24 studies in emergency contraception (3 repeated-dose and 21 single-dose studies).

Patient exposure

Over 6,200 subjects have been exposed to ulipristal acetate during its clinical development (completed studies, including PGL11-006 Part I) as an emergency contraceptive and as a treatment for uterine fibroids, including:

- 6,168 subjects for 5 mg and above for any duration,
- 4,999 subjects who have received a single dose,
- 1,238 subjects who have received repeated doses,
  - of whom 1,053 were exposed for ≥3 months to the target dose of 5 mg/day or higher,
  - of whom 541 subjects were exposed for ≥ two 3-month treatment courses to the target does of 5 mg/day or higher (which, when taking account of off-treatment intervals in studies PGL09-027 and PGL11-006, equates to about 9 months of treatment and monitoring),of whom 457 subjects were exposed to four 3-month treatment courses in completed study to 5 or 10 mg/day (which, when taking account of off-treatment intervals, equates to 21 months of treatment and monitoring).

In the ongoing Study PGL11-024 (PEARL extension 2), the extension of PGL09-027, 64 subjects have continued for further 4 additional treatment courses with ulipristal acetate 10 mg/day, and so far 53 have completed additional 4 courses (i.e. a total of 8 treatment courses).

Since the initial Marketing Authorisation in 2012 and at the cut-off date of 22 February 2015 (in line with next PSUR 06), Esmya marketing exposure is estimated at around 165,800 patients.

The study design and the number of subjects exposed to ulipristal acetate in the phase 3 studies are summarised in Table 15.

Table 15: Phase III repeated-dose studies with ulipristal acetate in subjects with symptomatic uterine fibroids (safety population)

Study	Design	Ulipristal acetate		Control		Planned Duration of treatment	Overall treatment and follow-up period
		5 mg/day	10 mg/day	Placebo	Active control		
		Number of subjects					
PGL07-021	Double-blind, placebo controlled	95	98	48	-	12 weeks	3 + 6 months
PGL07-022[a]	Double-blind, double-dummy, active comparator controlled	97	103	-	101	12 weeks	3 + 6 months
PGL09-026	Open-label	-	209	-	-	12 weeks	3 + 3 months
PGL09-027	Open-label	-	132[b]	-	-	Up to 3 additional courses of 12 weeks[c]	Approx. 18 + 3 months
PGL11-006	Double-blind, parallel groups	230	221	-	-	4 courses of 12 weeks[d]	Approx. 21 months

a Protocol specified two co-primary safety endpoints.

b 132 subjects (from the PGL09-026 population) were included in the safety population, but only 131 received ulipristal acetate during Study PGL09-027 (1 subject received placebo [double blind treatment] only instead of ulipristal acetate).

c Each course separated by 10 days of treatment with placebo or progestin [NETA] followed by a drug-free period.

d Each course separated by a drug-free period until the start of the second menstruation following the end of the previous treatment course.

A summary of the exposure to ulipristal acetate for ≥ 6 months (two or more intermittent 3-month treatment courses) in completed studies is presented in Table 16 below.

Table 16: Exposure to ulipristal acetate during its clinical development, completed studies (safety population) to support long-term use

Length of exposure	PGL-N-0090[a]		PGL09-027	PGL11-006		Total (5 mg and above)	ICH E1 requirement for long-term use
	10 mg	20 mg	10 mg	5 mg	10mg		
≥ 1 day	-	-	-	-	-	**6168**	**> 1500**
≥ 6 months i.e.2 courses (approx. 9 months elapsed time)	**1**	**5**	**128**	**207**	**200**	**541**	**300-600**
≥ 12 months i.e. 4 courses (approx. 21 months elapsed time)	-	-	**103**	**171**	**172**	**446**	**> 100**

a exposure 6 months continuously.

Demographic characteristics

Table 17: Demographic characteristics in Phase III studies

Variable Parameter	Study PGL07-021		Study PGL07-022		Study PGL09-026	Study PGL09-027	Study PG11-006 Part I	
	Ulipristal acetate		Ulipristal acetate		Ulipristal acetate	Ulipristal acetate	Ulipristal acetate	
	5 mg/day (N=95)	10 mg/day (N=98)	5 mg/day (N=97)	10 mg/day (N=103)	10 mg/day (N=209)	10 mg/day (N=132)	5 mg/day (N = 230)	10 mg/day (N = 221)
Race [N (%)]								
White	84 (88.4%)	87 (88.8%)	83 (85.6%)	88 (85.4%)	179 (85.6%)	121 (91.7%)	213 (92.6%)	212 (95.9%)
Black	0	0	9 (9.3%)	11 (10.7%)	19 (9.1%)	8 (6.1%)	12 (5.2%)	8 (3.6%)
Asian	11 (11.6%)	11 (11.2%)	1 (1.0%)	1 (1.0%)	3 (1.4%)	1 (0.8%)	1 (0.4%)	0
Hispanic	0	0	3 (3.1%)	2 (1.9%)	6 (2.9%)	2 (1.5%)	1 (0.4%)	0
Other	0	0	1 (1.0%)	1 (1.0%)	2 (1.0%)	0	2 (0.9%)	1 (0.5%)
Not reported	0	0	0	0	0	0	1 (0.4%)	0
Age [years] (n)	95	98	97	103	209	132	230	221
Mean (SD)	41.2 (5.9)	42.0 (5.5)	40.1 (6.2)	40.7 (6.3)	40.1 (6.0)	40.5 (5.8)	41.6 (5.4)	41.4 (5.1)
Min / Max	24 / 50	23 / 50	25 / 50	20 / 50	20 / 48	20 / 48	18 / 50	26 / 50
Height [cm] (n)	95	98	97	103	209	132	229	221
Mean (SD)	164.3 (6.5)	163.9 (6.1)	163.7 (6.4)	162.3 (6.7)	164.7 (5.9)	164.4 (5.8)	165.5 (6.1)	166.4 (5.7)
Min / Max	150 / 178	145 / 178	146 / 180	146 / 180	147 / 180	149 / 180	147 / 184	150 / 181
Weight [kg] (n)	95	98	97	103	209	132	229	221
Mean (SD)	70.1 (13.6)	67.1 (10.3)	68.3 (12.3)	68.8 (12.7)	69.0 (12.8)	68.7 (13.6)	69.17 (12.67)	69.98 (12.81)
Min / Max	42.0 / 120.0	48.9 / 95.0	48.5 / 108.0	46.0 / 111.0	41.0 / 110.0	41.0 / 110.0	45.5 / 116.7	47.0 / 117.0
BMI [kg/m²] (n)	95	98	97	103	209	132	229	221
Mean (SD)	25.9 (4.6)	25.0 (3.9)	25.4 (4.1)	26.2 (4.7)	25.4 (4.4)	25.4 (4.7)	25.20 (4.10)	25.27 (4.49)
Min / Max	18.1 / 39.2	18.1 / 37.6	19.4 / 37.8	18.1 / 39.8	18.0 / 39.8	18.0 / 39.8	18.0 / 38.1	17.9 / 39.5
Of Childbearing Potential [N (%)]	87 (91.6%)	92 (93.9%)	93 (95.9%)	99 (96.1%)	201 (96.2%)	129 (97.7%)	221 (96.1%)	206 (93.2%)

N = number of subjects per treatment group, n = number of subjects for whom data were available, BMI = body mass index, SD = standard deviation, min = minimum, max = maximum.

Adverse events

In Study PGL11-006 AEs were classified as:

- On-treatment TEAEs were defined as events whose start date was on or after the first dose of study medication, up to and including 7 days after the last dose of study medication within each treatment course. On-treatment TEAEs were summarised by treatment course.
- Off-treatment TEAEs were defined as those whose start date was more than 7 days after the last dose of study medication within each treatment course and prior to the start of the next treatment course. Off-treatment TEAEs were summarised by treatment course.

On-treatment TEAEs

The proportion of patients reporting on-treatment TEAEs was higher during the first treatment course (44.3% in both groups) than during the second treatment course (27.4% and 29.8% in the 5 mg/day group and 10 mg/day group, respectively). The most frequently reported on-treatment TEAE was headache followed by hot flush in both treatment courses 1 and 2.

The majority of TEAEs of headache were mild or moderate in intensity, with the exception of 3 severe events reported in 2 (0.9%) subjects. All the TEAEs of hot flush were mild or moderate in intensity. During treatment course 1, in addition to headache and hot flush, on-treatment TEAEs occurring at a frequency of ≥2% included influenza (in 3.8% of subjects), breast pain/tenderness/discomfort (in 2.7% of subjects), nausea (in 2.7% of subjects), nasopharyngitis and fatigue (both in 2.2% of subjects), and pelvic pain (in 2.0% of subjects). No other TEAEs occurred at a frequency of ≥2% in any treatment group during treatment course 2.

More on-treatment TEAEs were reported during treatment course 1 than during treatment courses 2, 3 and 4. In general, the number of subjects reporting on-treatment TEAEs by SOC and PT were similar for the PGL4001 5 mg and 10 mg groups.

Table 18: On-treatment Treatment Emergent Adverse Events occurring in ≥ 2% of patients presented by System Organ Class and Preferred Term (Study PGL11-006)

	Treatment Course 1						Treatment Course 2						Treatment Course 3						Treatment Course 4					
	PGL4001 5mg			PGL4001 10mg			PGL4001 5mg			PGL4001 10mg			PGL4001 5mg			PGL4001 10mg			PGL4001 5mg			PGL4001 10mg		
System Organ Class / PT	n	N	%	n	N	%	n	N	%	n	N	%	n	N	%	n	N	%	n	N	%	n	N	%
Number of subjects receiving study medication		230			221			215			205			193			188			180			174	
At Least One On-Treatment TEAE	233	102	44.3	236	98	44.3	114	59	27.4	95	60	29.3	44	32	16.6	56	38	20.2	58	43	23.9	59	33	19.0
Reproductive system and breast disorders	**35**	**31**	**13.5**	**33**	**30**	**13.6**	**21**	**17**	**7.9**	**15**	**14**	**6.8**	**9**	**9**	**4.7**	**16**	**15**	**8.0**	**16**	**14**	**7.8**	**16**	**12**	**6.9**
Hot flush	14	13	5.7	16	15	6.8	9	8	3.7	6	6	2.9	3	3	1.6	5	5	2.7	5	5	2.8	8	7	4.0
Breast pain/Breast tenderness/Breast discomfort#	7	7	3.0	5	5	2.3	2	2	0.9	0	0	0.0	0	0	0.0	1	1	0.5	1	1	0.6	2	2	1.1
Pelvic pain	5	5	2.2	4	4	1.8	4	4	1.9	1	1	0.5	1	1	0.5	0	0	0.0	2	2	1.1	0	0	0.0
Vaginal discharge	3	3	1.3	3	3	1.4	2	2	0.9	2	2	1.0	1	1	0.5	3	3	1.6	2	2	1.1	0	0	0.0
Infections and infestations	**32**	**31**	**13.5**	**35**	**31**	**14.0**	**13**	**13**	**6.0**	**16**	**13**	**6.3**	**6**	**5**	**2.6**	**14**	**12**	**6.4**	**12**	**11**	**6.1**	**11**	**8**	**4.6**
Influenza	9	9	3.9	8	8	3.6	0	0	0.0	1	1	0.5	1	1	0.5	0	0	0.0	3	3	1.7	2	2	1.1
Nasopharyngitis	2	2	0.9	8	8	3.6	3	3	1.4	1	1	0.5	2	1	0.5	2	2	1.1	2	2	1.1	2	2	1.1
Cystitis	1	1	0.4	3	3	1.4	1	1	0.5	0	0	0	1	1	0.5	2	2	1.1	1	1	0.6	1	1	0.6
Tonsillitis	4	4	1.7	2	2	0.9	1	1	0.5	1	1	0.5	0	0	0.0	1	1	0.5	0	0	0.0	1	1	0.6
Nervous system disorders	**37**	**30**	**13.0**	**43**	**26**	**11.8**	**19**	**16**	**7.4**	**13**	**9**	**4.4**	**5**	**4**	**2.1**	**5**	**5**	**2.7**	**6**	**6**	**3.3**	**5**	**4**	**2.3**
Headache	28	23	10.0	36	24	10.9	15	13	6.0	8	6	2.9	5	4	2.1	5	5	2.7	4	4	2.2	5	4	2.3
Gastrointestinal disorders	**32**	**27**	**11.7**	**26**	**22**	**10.0**	**5**	**4**	**1.9**	**6**	**6**	**2.9**	**1**	**1**	**0.5**	**3**	**3**	**1.6**	**6**	**6**	**3.3**	**7**	**6**	**3.4**
Nausea	8	8	3.5	4	4	1.8	0	0	0.0	0	0	0	0	0	0.0	0	0	0	1	1	0.6	2	2	1.1
Abdominal pain	4	3	1.3	1	1	0.5	1	1	0.5	0	0	0.0	0	0	0.0	1	1	0.5	2	2	1.1	3	3	1.7
Investigations	**16**	**11**	**4.8**	**13**	**10**	**4.5**	**5**	**5**	**2.3**	**6**	**4**	**2.0**	**3**	**3**	**1.6**	**1**	**1**	**0.5**	**3**	**3**	**1.7**	**3**	**3**	**1.7**
Blood creatine phosphokinase increased	5	4	1.7	1	1	0.5	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0	1	1	0.6	1	1	0.6
Weight increased	2	2	0.9	2	2	0.9	1	1	0.5	0	0	0.0	2	2	1.0	1	1	0.5	0	0	0.0	0	0	0.0
Musculoskeletal and connective tissue disorders	**13**	**10**	**4.3**	**8**	**8**	**3.6**	**11**	**8**	**3.7**	**2**	**2**	**1.0**	**2**	**2**	**1.0**	**3**	**3**	**1.6**	**5**	**5**	**2.8**	**3**	**3**	**1.7**
Back pain	3	2	0.9	3	3	1.4	2	2	0.9	0	0	0.0	0	0	0.0	1	1	0.5	2	2	1.1	2	2	1.1

	Treatment Course 1						Treatment Course 2						Treatment Course 3						Treatment Course 4					
	PGL4001 5mg			PGL4001 10mg			PGL4001 5mg			PGL4001 10mg			PGL4001 5mg			PGL4001 10mg			PGL4001 5mg			PGL4001 10mg		
System Organ Class / PT	n	N	%	n	N	%	n	N	%	n	N	%	n	N	%	n	N	%	n	N	%	n	N	%
General disorders and administration site conditions	**10**	**10**	**4.3**	**14**	**13**	**5.9**	**8**	**6**	**2.8**	**4**	**3**	**1.5**	**2**	**2**	**1.0**	**1**	**1**	**0.5**	**2**	**2**	**1.1**	**4**	**4**	**2.3**
Fatigue	3	3	1.3	7	7	3.2	4	4	1.9	2	2	1.0	0	0	0.0	1	1	0.5	1	1	0.6	1	1	0.6
Skin and subcutaneous tissue disorders	**10**	**9**	**3.9**	**12**	**9**	**4.1**	**8**	**8**	**3.7**	**6**	**6**	**2.9**	**3**	**3**	**1.6**	**1**	**1**	**0.5**	**3**	**3**	**1.7**	**1**	**1**	**0.6**
Acne	4	4	1.7	5	4	1.8	2	2	0.9	1	1	0.5	1	1	0.5	0	0	0.0	0	0	0.0	0	0	0.0
Psychiatric disorders	**12**	**11**	**4.8**	**12**	**9**	**4.1**	**6**	**5**	**2.3**	**3**	**3**	**1.5**	**2**	**2**	**1.0**	**1**	**1**	**0.5**	**2**	**2**	**1.1**	**1**	**1**	**0.6**
Anxiety	3	2	0.9	3	3	1.4	0	0	0.0	0	0	0.0	2	2	1.0	1	1	0.5	1	1	0.6	0	0	0.0
Respiratory, thoracic and mediastinal disorders	**1**	**1**	**0.4**	**10**	**9**	**4.1**	**1**	**1**	**0.5**	**6**	**5**	**2.4**	**2**	**2**	**1.0**	**0**	**0**	**0.0**	**0**	**0**	**0.0**	**2**	**2**	**1.1**
Cough	1	1	0.4	5	4	1.8	0	0	0.0	2	2	1.0	1	1	0.5	0	0	0.0	0	0	0.0	1	1	0.6
Oropharyngeal pain	0	0	0.0	3	3	1.4	0	0	0.0	1	1	0.5	0	0	0.0	0	0	0.0	0	0	0.0	1	1	0.6
Vascular disorders	**6**	**6**	**2.6**	**4**	**4**	**1.8**	**3**	**3**	**1.4**	**1**	**1**	**0.5**	**1**	**1**	**0.5**	**0**	**0**	**0.0**	**2**	**2**	**1.1**	**1**	**1**	**0.6**
Hypertension	3	3	1.3	3	3	1.4	1	1	0.5	1	1	0.5	0	0	0.0	0	0	0.0	1	1	0.6	0	0	0.0
Metabolism and nutrition disorders	**4**	**3**	**1.3**	**3**	**3**	**1.4**	**2**	**2**	**0.9**	**4**	**4**	**2.0**	**0**	**0**	**0.0**	**1**	**1**	**0.5**	**0**	**0**	**0.0**	**1**	**1**	**0.6**
Blood and lymphatic system disorders	**9**	**9**	**3.9**	**3**	**3**	**1.4**	**0**	**0**	**0.0**	**1**	**1**	**0.5**	**1**	**1**	**0.5**	**0**	**0**	**0.0**	**0**	**0**	**0.0**	**0**	**0**	**0.0**
Anaemia	6	6	2.6	2	2	0.9	0	0	0.0	1	1	0.5	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
Injury, poisoning and procedural complications	**1**	**1**	**0.4**	**4**	**3**	**1.4**	**2**	**1**	**0.5**	**1**	**1**	**0.5**	**2**	**1**	**0.5**	**1**	**1**	**0.5**	**0**	**0**	**0.0**	**3**	**3**	**1.7**
Renal and urinary disorders	**2**	**2**	**0.9**	**2**	**2**	**0.9**	**3**	**3**	**1.4**	**2**	**2**	**1.0**	**1**	**1**	**0.5**	**3**	**2**	**1.1**	**1**	**1**	**0.6**	**0**	**0**	**0.0**
Ear and labyrinth disorders	**7**	**7**	**3.0**	**3**	**3**	**1.4**	**2**	**2**	**0.9**	**1**	**1**	**0.5**	**0**	**0**	**0.0**	**0**	**0**	**0.0**	**0**	**0**	**0.0**	**0**	**0**	**0.0**
Vertigo	6	6	2.6	2	2	0.9	1	1	0.5	1	1	0.5	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
Cardiac disorders	**1**	**1**	**0.4**	**4**	**4**	**1.8**	**2**	**2**	**0.9**	**1**	**1**	**0.5**	**1**	**1**	**0.5**	**0**	**0**	**0.0**	**0**	**0**	**0.0**	**0**	**0**	**0.0**
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**0**	**0**	**0.0**	**1**	**1**	**0.5**	**0**	**0**	**0.0**	**2**	**2**	**1.0**	**1**	**1**	**0.5**	**3**	**3**	**1.6**	**0**	**0**	**0.0**	**1**	**1**	**0.6**

n = No. of Events, N = No. of Subjects with Event, % = 100*(No. of Subjects with Event/No. of Subjects). PT = Preferred Term

TEAE: Treatment emergent adverse events are defined as events whose start date is on or after the first dose of study medication.
On-treatment TEAEs are defined as events whose start date is on or after the first dose of study medication, up to and including 7 days after the last dose of study medication within each treatment course.
Denominator of percentage is the number of subjects receiving study medication within each treatment course.

The number of subjects and events reporting preferred terms of 'breast pain', 'breast tenderness' and 'breast discomfort' have been combined as one preferred term of 'breast pain / breast tenderness / breast discomfort'

Source: Table 14.3.1.3

Off-treatment TEAEs

In Study PGL11-006 Part I, a total of 169 off-treatment TEAEs were reported in 106 (23.5%) patients with similar frequency in the two treatment groups. Off-treatment periods went from >7 days after the last dose of treatment course 1 to the beginning of treatment course 2, and from >7 days after the last dose of

treatment course 2 to Visit 8. Fewer off-treatment TEAEs were reported following treatment course 2 than treatment course 1.

The only TEAEs reported in more than 2% of patients during any off-treatment interval were dysmenorrhoea (in 5 [2.2%] and 8 [3.6%] subjects in the 5 mg/day and 10 mg/day groups, respectively) and menorrhagia (in 8 [3.5%] and 3 [1.4%] subjects in the 5 mg/day and 10 mg/day groups, respectively). The TEAEs were mainly mild or moderate in severity. Six (1.3%) subjects experienced severe events, all of which were also SAEs.

Following treatment course 4, including the time up to the end of study follow-up visit (visit 12), dysmenorrhoea was reported by 4 and 8 (4.6%) subjects from the PGL4001 5 mg and 10 mg groups, respectively, and headache by 4 and 1 subjects from the PGL4001 5 mg and 10 mg groups, respectively; no other TEAEs were reported with a frequency of ⩾2%.

The number of subjects reporting off-treatment TEAEs by SOC and PT were similar for the PGL4001 5 mg and 10 mg groups. More off-treatment TEAEs were reported following treatment courses 1 and 4, than following treatment courses 2 and 3.

Treatment–Related Adverse Events

Overall, 259 on-treatment adverse events in 112 (24.8%) subjects were considered by the Investigators to be ulipristal acetate-related in study PGL11-006 Part I. None of the treatment-related TEAEs were SAEs.

Table 19: On-Treatment, TEAEs Occurring in ≥2% of Subjects in any Treatment Course Presented by System Organ Class, Preferred Term, Treatment Course and Treatment Group (Safety Set, Study PGL11-006)

	Treatment Course 1						Treatment Course 2						Treatment Course 3						Treatment Course 4					
	PGL4001 5mg			PGL4001 10mg			PGL4001 5mg			PGL4001 10mg			PGL4001 5mg			PGL4001 10mg			PGL4001 5mg			PGL4001 10mg		
System Organ Class / Preferred Term	n	N	%	n	N	%	n	N	%	n	N	%	n	N	%	n	N	%	n	N	%	n	N	%
Number of subjects receiving study medication		230			221			215			205			193			188			180			174	
At Least One Study Medication Related On-Treatment TEAE	89	47	20.4	94	43	19.5	45	28	13.0	30	22	10.7	14	9	4.7	12	12	6.4	13	11	6.1	20	14	8.0
Reproductive system and breast disorders	**27**	**23**	**10.0**	**24**	**21**	**9.5**	**13**	**11**	**5.1**	**11**	**11**	**5.4**	**4**	**4**	**2.1**	**7**	**7**	**3.7**	**8**	**7**	**3.9**	**10**	**8**	**4.6**
Hot flush	13	12	5.2	15	14	6.3	9	8	3.7	6	6	2.9	3	3	1.6	5	5	2.7	5	5	2.8	8	7	4.0
Breast pain/Breast tenderness/Breast discomfort#	3	3	1.3	5	5	2.3	0	0	0.0	0	0	0.0	0	0	0.0	1	1	0.5	1	1	0.6	1	1	0.6
Nervous system disorders	**11**	**11**	**4.8**	**14**	**10**	**4.5**	**7**	**7**	**3.3**	**4**	**2**	**1.0**	**4**	**3**	**1.6**	**2**	**2**	**1.1**	**1**	**1**	**0.6**	**2**	**2**	**1.1**
Headache	10	10	4.3	11	10	4.5	6	6	2.8	0	0	0.0	4	3	1.6	2	2	1.1	1	1	0.6	2	2	1.1
Skin and subcutaneous tissue disorders	**9**	**8**	**3.5**	**11**	**8**	**3.6**	**6**	**6**	**2.8**	**6**	**5**	**2.4**	**3**	**3**	**1.6**	**0**	**0**	**0.0**	**2**	**2**	**1.1**	**1**	**1**	**0.6**
Acne	4	4	1.7	5	4	1.8	2	2	0.9	1	1	0.5	1	1	0.5	0	0	0.0						
Gastrointestinal disorders	**13**	**12**	**5.2**	**14**	**11**	**5.0**	**2**	**2**	**0.9**	**0**	**0**	**0.0**	**0**	**0**	**0.0**	**0**	**0**	**0.0**	**1**	**1**	**0.6**	**3**	**2**	**1.1**
Nausea	4	4	1.7	4	4	1.8	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0	1	1	0.6
General disorders and administration site conditions	**6**	**6**	**2.6**	**7**	**6**	**2.7**	**5**	**4**	**1.9**	**1**	**1**	**0.5**	**0**	**0**	**0.0**	**1**	**1**	**0.5**	**0**	**0**	**0.0**	**1**	**1**	**0.6**
Fatigue	2	2	0.9	5	5	2.3	2	2	0.9	1	1	0.5	0	0	0.0	1	1	0.5	0	0	0.0	1	1	0.6
Psychiatric disorders	**6**	**6**	**2.6**	**6**	**4**	**1.8**	**3**	**3**	**1.4**	**3**	**3**	**1.5**	**0**	**0**	**0.0**	**0**	**0**	**0.0**	**1**	**1**	**0.6**	**0**	**0**	**0.0**
Investigations	**4**	**4**	**1.7**	**8**	**6**	**2.7**	**1**	**1**	**0.5**	**2**	**1**	**0.5**	**1**	**1**	**0.5**	**0**	**0**	**0.0**	**0**	**0**	**0.0**	**1**	**1**	**0.6**

n = No. of events, N = No. of subjects with event, % = 100*(No. of subjects with event/No. of subjects).
TEAE: Treatment emergent adverse events are defined as events whose start date is on or after the first dose of study medication.
On-treatment TEAEs are defined as events whose start date is on or after the first dose of study medication, up to and including 7 days after the last dose of study medication within each treatment course.
Denominator of percentage is the number of subjects receiving study medication within each treatment course.
The number of subjects and events reporting the PTs of 'breast pain', 'breast tenderness' and 'breast discomfort' have been combined as one PT of 'breast pain/breast tenderness/breast discomfort'.
Source: Table 14.3.1.5

Adverse drug reactions

The main outputs used for determining the nature and incidence of adverse drug reactions (ADRs) were the pooled table of treatment-related adverse events (AE's) reported during study treatment in phase III clinical studies (PEARL I-II, III and IV). The data from the Phase III studies were pooled to increase the precision of the adverse drug reactions rates. When reviewing AE's reported during the Phase III trials, it became

apparent that there was only a slight difference in the overall incidence of AE's between subjects receiving ulipristal acetate 5 mg once daily or 10 mg once daily. Therefore, it was decided to pool data from the 5 mg and 10 mg treatment groups for the purpose of calculating the overall incidence of ADRs. When comparing repeated treatment courses, overall adverse reactions rate was less frequent in subsequent treatment courses than during the first one and each adverse reaction was less frequent or remained in the same frequency category (except for dyspepsia and genital discharge who were classified as uncommon in treatment course 3 based on one subject occurrence). Hence, the highest potential frequency of adverse drug reactions for any given 3-month course (i.e. frequency of treatment course 1) is presented in the SmPC.

All on-treatment AEs for ulipristal acetate reported as treatment related by the investigators were reviewed and a thorough causality assessment between the medicinal product and the AE was made, taking into account at least a reasonable possibility of causal relationship. All AEs reported by the clinical investigators as treatment related were considered to be ADRs unless any of the following pertained: The ADR was reported at same or higher rate in patients receiving placebo in study PGL07-021 than in patients receiving ulipristal acetate; The ADR was reported at a higher rate in the comparator arm of study PGL07-022, and there were no event in the ulipristal acetate treatment groups in study PGL07-021; The ADR was subsequently found to be a misdiagnosis, and it was more appropriate to include a different AE term; The ADR was related to an underlying medical history or a laboratory test, abnormality, and review of all available laboratory data did not confirm any signals or trends of abnormal values in the ulipristal acetate treatment groups. For few cases, if the particular event was reported for one subject only in the entire Phase III database in ulipristal acetate groups, it was excluded if it comprised terms relating to natural disease progression, or medical judgment indicated that a relationship to ulipristal acetate was implausible; In addition, there were many isolated cases of different AE terms in the system, organ class (SOC), "Infections and Infestations" randomly but evenly distributed across treatment groups. The incidence rate of those AE terms was similar or lower to placebo or comparator group and all AEs in this SOC were excluded.

No new adverse drug reactions were detected based on safety data from study PGL11-006. The frequency of the following ADRs was revised based on the crude incidence rate in the pooled ADRs reported by investigators with both doses of ulipristal acetate across three Phase III studies: Epistaxis, Dyspepsia, Flatulence, Hyperhidrosis, Ovarian cyst ruptured, Breast swelling, Uterine haemorrhage, Oedema, Weight increased, Blood cholesterol increased.

Adverse Events of Special Interest

Reproductive and Breast Disorders

In Study PGL11-006 Part I, TEAEs from the reproductive system and breast disorders SOC were the most common on-treatment TEAEs during treatment course 2 while during treatment course 1 TEAEs from the nervous system were more common. Overall, TEAEs from the reproductive system and breast disorder SOC were reported in more subjects during treatment course 1 than in treatment course 2. Hot flush was the TEAE most frequently reported. Among the off-treatment TEAEs, those from the reproductive and breast disorders SOC were always the most common. The most frequently reported TEAEs were dysmenorrhea followed by menorraghia.

Breast Disorders

Breast pain was the only breast disorder occurring in ≥ 1% of subjects during treatment course 1. During treatment course 2, breast pain was reported only in the 5 mg/day group (in 0.9% of patients).

Excessive Uterine Bleeding

In Study PGL11-006 Part I, over the 2 repeated intermittent treatment courses, 21 subjects out of 451 subjects included, reported 24 AEs related to bleeding, of which 5 were SAEs and occurred in the off-drug

interval at the time when menstruation is expected. These AEs were mainly metrorrhagia and menorrhagia. In addition, one SAE of heavy menstrual bleeding was reported from ongoing PGL11-006 Part II after third treatment course.

The frequency of TEAEs related to excessive uterine bleeding did not increase with the number of treatment courses in Studies PGL09-027 and Study PGL11-006. TEAEs were reported in:

- 4 (3.1%) subjects in Study PGL09-027 and 11 (2.6%) subjects (7 [3.2%] and 4 [2.0%] in the 5 mg/day and 10 mg/day groups, respectively) in Study PGL11-006 during and after treatment course 2,
- 2 (1.7%) subjects in Study PGL09-027 during and after treatment course 3,
- 2 (1.9%) subjects in Study PGL09-027 during and after treatment course 4.

Endometrial Hyperplasia and Hypertrophy

In Study PGL11-006 Part I, TEAEs of endometrial hyperplasia were reported in 1 (0.2%) subject during treatment course 1 with 5 mg, and in 4 (0.9%) subjects (off-treatment after the treatment course 1 with 5 mg/day), from those 4, only 1 diagnosis was confirmed by expert pathologists. Endometrial hypertrophy was reported as off-treatment TEAE in 1 subject in the 10 mg/day group (after treatment course 1). Results of endometrial biopsies and effects of treatment on endometrial thickness are discussed in more detail below.

Hot Flushes and Other Castration-Related Symptoms

In Study PGL11-006 Part I, castration-related TEAEs were hot flush, depression, depressive mood, decreased libido and vaginal infection. Hot flush was overall reported as on-treatment TEAE in 34 (7.5%) subjects (8 of them experienced hot flush in both treatment courses). Depression was overall reported in 5 (1.1%) subjects and depressive mood in 3 (0.7%) subjects. Decreased libido was overall reported in 3 (0.7%) subjects, vaginal infection in 2 (0.4%) subjects.

There was no trend of an increase in castration-related TEAEs with repeated courses of treatment with ulipristal acetate, similar to observations in Study PGL09-027.

Ovarian Cysts

In Study PGL11-006 Part I, the presence of cysts was assessed by transvaginal ultrasound at screening 3, Visits 6, 7 and 8. Overall, normal ovaries were observed for >89% of subjects at all visits. Follicular cysts seen on 2 or more consecutive visits were observed for 7 subjects in the 5 mg/day group and for 7 subjects in the 10 mg/day group.

One subject in the 5 mg/day group had endometrioma on the left ovary reported at Visit 6, at an unscheduled visit 1 month later, and at early termination visit 2 weeks later. This was clinically significant and reported as a TEAE of ovarian cyst, was treated with surgery and resolved 2 months later. Another subject in the 5 mg/day group had endometrioma on the right ovary at screening (considered as clinically significant) and at Visit 6 (considered as non-clinically significant), but was reported as having a normal transvaginal ultrasound of ovaries thereafter.

One subject in the 10 mg/day group had a moderate TEAE of ovarian cyst during treatment course 2 that was considered related to study treatment. In addition, a total of 4 off-treatment TEAEs of ovarian cysts were reported in 4 subjects. All these events resolved, two were considered as related to the treatment (1 subject in the 5 mg/day group).

Dysmenorrhea

Dysmenorrhea was overall reported in 2 subjects in study PGL11-006 Part I: 1 subject in the 5 mg/day group during treatment course 1 and 1 subject in the 10 mg/day group during treatment course 2. Off-treatment TEAEs of dysmenorrhoea were more common than on-treatment TEAEs. Dysmenorrhoea was reported in 13 (2.9%) subjects overall, 10 after treatment course 1 and 4 after treatment course 2.

Acne

Twelve TEAEs of acne were overall reported in 9 (2.0%) subjects in study PGL11-006 Part I. The TEAEs of acne reported were mild or moderate in severity and all of them were considered as treatment-related. No off-treatment TEAEs of acne were reported in any treatment group.

Nervous System Disorders

In study PGL11-006 Part I, headache was the most frequently reported on-treatment TEAE for both treatment courses 1 and 2, but the proportion of subjects experiencing headache was higher in treatment course 1 (overall 9.8%) than in treatment course 2 (overall 4.3%). None of the TEAEs of headache were serious and the majority were mild or moderate in intensity, with 3 severe events in 2 subjects.

Cardiac and Vascular Disorders

In study PGL11-006 Part I, the incidence of TEAEs from the cardiac and vascular disorders SOCs was low. The most common TEAE was hypertension (reported in treatment course 1 in > 1% of subjects in both treatment groups). These were reported as hypertension, although no data are available to assess whether these were confirmed hypertension cases versus single occurrence of high blood pressure.

Results of vital sign and ECG monitoring did not raise any concerns regarding cardiac safety.

Gastrointestinal Disorders

The most common gastrointestinal TEAE was nausea, followed by abdominal pain and toothache in study PGL11-006 Part I. The incidence was lower during treatment course 2 than during treatment course 1.

Hepatobiliary Disorders and Liver Safety

On-treatment TEAEs from the hepatobiliary disorders SOC were reported only in the 10 mg/day group (study PGL11-006 Part I). Two events of cholelithiasis were reported in 2 subjects during treatment course 1 and 2 events of liver disorders were reported in 1 subject during treatment course 1 and 1 subject during treatment course 2. In the investigations SOC, a few cases of on-treatment TEAEs related to abnormal liver function were reported, with increases in ALT, gamma-GT, AST and blood alkaline phosphatase. The majority of these events were reported during treatment course 1. No cases of hepatobiliary disorders were reported after treatment course 3 and 4.

Endometrial safety

Endometrial thickness

Endometrial thickness was measured by ultrasound in Study PGL11-006, at screening, 10-18 days after start of menses following treatment course 1 (Visit 6), in the last 8 days of treatment course 2 (Visit 7) and 10-18 days after start of menses following treatment course 2 (Visit 8).

The mean endometrial thickness was similar at all visits including screening, ranging from 8.4 to 8.8 in the 5 mg/day group and from 7.9 to 9.5 in the 10 mg/day group. The number of subjects with a thickness >16 mm rose from 22 (4.9%) subjects at screening to 31 (7.4%) subjects at Visit 6 (10 to 18 days after start of menstruation following end of treatment course 1), before returning to levels similar to screening at Visit 7 (20 [4.9%] at the end of treatment course 2), and decreasing to 13 (3.4%) subjects at Visit 8 (10 to

18 days after start of menstruation following end of treatment course 2). There were no major differences between the two treatment groups in terms of endometrial thickness.

Endometrial hypertrophy was reported as an off-treatment TEAE in 1 subject in the 10 mg/day group (after treatment course 1).

The individual endometrial thickness values over time for subjects (n=42) with an endometrial thickness ≤ 16 mm at screening and at least one assessment of endometrial thickness > 16 mm post-screening were also presented for the safety population (study PGL11-006 Part I). Subjects had occasionally an endometrial thickness > 16 mm. As expected, some subjects have an increased thickness after 1 course of treatment (Visit 6) but return to normal thickness after 2 courses of treatment (Visit 7). Some subjects presented still with normal endometrial thickness after 1 course of treatment, an increased thickness after 2 courses and came back to normal thickness after one menstruation post treatment (visit 8). Only three subjects had an endometrial thickness > 16 mm at all visits up to Visit 8. The MAH carefully looked at the data after Visit 8 of these individual patients (PGL11-006 ongoing Part II). The endometrial thickness of all 3 subjects ultimately decreased < 16 mm, at Visit 9 for 2 of them and Visit 10 for the last subject.

The final CSR was provided during the procedure. Endometrial safety data for Part I and Part II are summarised in the table below.

Table 20: Summary of Endometrium Thickness Data PGL11-006 (Safety Set)

Visit		Value (mm)	Treatment Group		
			PGL4001 5 mg (N=230)	PGL4001 10 mg (N=221)	Total (N=451)
Screening 3	Endometrium Thickness	N	225	220	445
		Mean	8.4	8.4	8.4
		SD	3.9	3.9	3.9
		Median	8.0	8.0	8.0
		Min, Max	2, 23	2, 27	2, 27
		>16mm	**11 (4.9%)**	**11 (5.0%)**	**22 (4.9%)**
Visit 6	Endometrium Thickness	N	214	207	421
		Mean	8.8	9.5	9.1
		SD	4.3	4.8	4.5
		Median	8.0	8.0	8.0
		Min, Max	1, 25	1, 29	1, 29
		>16mm	**13 (6.1%)**	**18 (8.7%)**	**31 (7.4%)**
Visit 7	Endometrium Thickness	N	207	200	407
		Mean	8.7	7.9	8.3
		SD	4.9	4.4	4.7
		Median	8.0	7.0	8.0
		Min, Max	1, 34	1, 35	1, 35
		>16mm	**13 (6.3%)**	**7 (3.5%)**	**20 (4.9%)**
Visit 8	Endometrium Thickness	N	192	193	385
		Mean	8.3	8.1	8.3
		SD	3.8	4.3	4.1
		Median	8.0	8.0	8.0
		Min, Max	2, 27	2, 37	2, 37
		>16mm	**7 (3.6%)**	**6 (3.1%)**	**13 (3.4%)**
Visit 9	Endometrium Thickness	N	182	180	362
		Mean	8.3	7.7	8.0
		SD	4.1	3.7	3.9
		Median	8.0	7.0	7.0
		Min, Max	1, 26	1, 32	1, 32
		>16mm	**7 (3.8%)**	**3 (1.7%)**	**10 (2.8%)**
Visit 10	Endometrium Thickness	N	172	169	341
		Mean	7.7	7.6	7.6
		SD	4.5	4.5	4.5
		Median	7.0	7.0	7.0
		Min, Max	0, 31	0, 40	0, 40
		>16mm	**9 (5.2%)**	**5 (3.0%)**	**14 (4.1%)**
Visit 11	Endometrium Thickness	N	170	164	334
		Mean	7.8	7.4	7.6
		SD	3.7	3.3	3.5
		Median	7.0	7.0	7.0
		Min, Max	0, 24	2, 30	0, 30
		>16mm	**4 (2.4%)**	**1 (0.6%)**	**5 (1.5%)**
Visit 12	Endometrium Thickness	N	166	168	334
		Mean	7.4	7.9	7.7
		SD	3.3	5.2	4.4
		Median	7.0	7.0	7.0
		Min, Max	1, 21	2, 64	1, 64
		>16mm	**1 (0.6%)**	**2 (1.2%)**	**3 (0.9%)**

Denominator of percentage is the number of subjects that have endometrium thickness measured at each visit.
Source: Table 54 CSR PGL11-006

Visit 6 = 10-18 days after start of menses following treatment course 1.
Visit 7 = End of treatment course 2.
Visit 8 = 10-18 days after start of menses following treatment course 2.
SD = standard deviation, N = number of subjects.

Data on endometrial thickness after more than 2 treatment courses with ulipristal acetate are available from Study PGL09-027.

Table 21: Analysis of endometrium thickness (Study PGL09-027)

		Ulipristal acetate 10mg/day		
		Placebo (N=69)	NETA (N =63)	Total (N=132)
Screening [a]	N	67	62	129
	> 16 mm, n (%)	3 (4.5)	-	3 (2.3)
	Mean (SD)	9.9 (4.8)	8.6 (2.9)	9.3 (4.0)
Visit 5 [a]	N	68	62	130
	> 16 mm, n (%)	8 (11.8)	2 (3.2)	10 (7.7)
	Mean (SD)	10.1 (4.6)	8.8 (4.3)	9.4 (4.5)
Visit 6 [a]	N	68	61	129
	> 16 mm, n (%)	9 (13.2)	2 (3.3)	11 (8.5)
	Mean (SD)	10.4 (4.7)	7.8 (3.6)	9.1 (4.4)
Visit B	N	62	58	120
	> 16 mm, n (%)	4 (6.5)	-	4 (3.3)
	Mean (SD)	9.5 (4.5)	7.9 (2.7)	8.8 (3.8)
Visit C	N	57	50	107
	> 16 mm, n (%)	1 (1.8)	-	1 (0.9)
	Mean (SD)	8.4 (3.5)	7.5 (3.1)	8.0 (3.4)
Visit D	N	51	44	95
	> 16 mm, n (%)	1 (2.0)	-	1 (1.1)
	Mean (SD)	7.7 (3.6)	7.2 (3.3)	7.5 (3.4)
Visit F	N	51	46	97
	> 16 mm, n (%)	1 (2.0)	1 (2.2)	2 (2.1)
	Mean (SD)	8.8 (3.5)	9.0 (2.9)	8.9 (3.2)

a part of PGL09-026 study.
Visit 5 = end of ulipristal acetate treatment course 1.
Visit 6 = 10-18 days after start of menstruation following treatment course 1, Part of PGL09-026 Study.
Visit B = 10-18 days after start of menses following treatment course 2.
Visit C = 10-18 days after start of menses following treatment course 3.
Visit D= end of ulipristal acetate treatment course 4.
Visit F = follow-up visit after end of treatment course 4.
SD = standard deviation, N = number of subjects.

Endometrial biopsies

Endometrial biopsies were performed in Study PGL11-006 at screening, approximately 4 weeks after baseline if screening biopsy was not adequate (Visit 3) and 10-18 days after start of menses following treatment course 2 (Visit 8).

All biopsies in Phase III studies were reviewed by the same three expert pathologists from the original workshop (NICHD sponsored workshop performed in 2006 to address “Progesterone Receptor Modulators and the Endometrium”) using a form designed to facilitate reporting of PAEC. The pathologists were blinded to treatment and timing of biopsy collection, as well as diagnosis made by their colleagues.

The pathologists used a rating scale to assess the endometrium biopsies, which required the following:

- judge whether the specimens were adequate or not,
- make a primary diagnosis of either benign endometrium (further classified as atrophy, inactive, proliferative, secretory, menstrual or non-physiological), hyperplasia (further classified as simple or complex atypical or non-atypical) or malignant neoplasm (further classified as endometrial adenocarcinoma or other malignant neoplasm),

- observe whether polyps were absent or present (if present, further classified as benign, hyperplastic or carcinomatous).

Only one pathologist was required to find a specimen adequate for it to be included in the analysis. For the primary diagnosis and the observation of polyps, the main diagnosis reported was the consensus of opinion of at least 2 out of 3 pathologists, or, if all pathologists reported a different finding, the most severe diagnosis was reported. After making the primary diagnosis, the pathologists were required to assess whether there were any non-physiological changes, and to describe these.

The biopsy taken at screening was read by a pathologist at the Central Clinical Laboratory to confirm eligibility. Results were then sent back to the site. If the screening endometrium biopsy results were not available at visit 2, the Investigator was told to contact the Clinical Research Associate who provided instructions on how to document and, if applicable, proceed with the inclusion of the subject. If the screening biopsy was taken but confirmed as not adequate by the Central Clinical Laboratory (because of no tissue or endocervical tissue or technically inadequate) at the time of inclusion, the subject was requested to repeat the biopsy at visit 3.

Visit 8, visit 11 and visit 12 biopsies were also read by a pathologist at the Central Clinical Laboratory. Results were communicated to the site immediately in case of atypia or adenocarcinoma.

In order to get a better understanding of the reversibility of PAECs after the end of treatment, biopsies were taken after one menstrual bleed after end of treatment (visit 8 and visit 11) and at the follow-up visit (visit 12).

Results from Part I and Part II of Study PGL11-006

In Study PGL11-006 prior to inclusion, of 555 subjects screened, 8 subjects (1.44%) were excluded from the study prior to treatment start due to a diagnosis of endometrial hyperplasia. Overall, 451 subjects started the first treatment course.

At screening in Study PGL11-006, a total of 450 of 451 subjects provided an endometrium biopsy and, of these, 422 (93.8%) were considered adequate for histology review. Endometrium biopsy consensus review provided a diagnosis of benign endometrium for all (100%) samples; the only other observations were benign polyps in 7 (1.7%) subjects.

The final CSR included 293 adequate biopsies taken after 4 treatment courses (Visit 11) and 286 adequate biopsies taken 3 months after the end of the fourth and last 3- month treatment course (Visit 12). Cases of hyperplasia/malignant neoplasia diagnosed by consensus in adequate biopsies in study PGL11-006 are presented in table 23.

In addition to cases of hyperplasia captured at nominated protocol visits, one consensus diagnosis of simple atypical hyperplasia was reported following the unscheduled histology review of material taken by curettage following the SAE of menorrhagia following treatment course 1. At early termination visit approximately 1 month later this subject had a consensus diagnosis of benign endometrium.

Overall, 6 cases of hyperplasia were diagnosed in 451 subjects treated with ulipristal acetate 5 or 10 mg and undergoing repeated endometrium biopsies:

- For one subject, hyperplasia (simple atypical) was diagnosed after menstruation following end of treatment course 1. The subject discontinued study and a control biopsy at early termination visit, a month later showed benign endometrium.

- For three subjects, hyperplasia (simple atypical, simple non- atypical, simple non-atypical) were diagnosed after menstruation following end of treatment course 2 (V8). Subjects continued in the study and

received two additional 3-months treatment courses. All three subject's next biopsy (V11) indicated full disappearance of hyperplasia.

- For one subject, hyperplasia (complex atypical) was diagnosed after return of menstruation following end of-treatment course 4 (V11), she continued in the study and a control biopsy three months after treatment completion (V12) showed benign endometrium.

- For one subject, hyperplasia (complex non-atypical) was diagnosed 3 months following end of treatment course 4 (V12), therefore at end of study. Of note, at previous biopsy performed after return of menstruation following end of treatment course 4 (V11), her endometrium was rated as "benign endometrium" by all central and expert pathologists.

No particular pathologic bleeding pattern for subjects could be identified for the 6 cases of hyperplasia. No endometrium thickening above 16 mm was reported for any of these 6 subjects at the time of hyperplasia diagnosis. There was generally a good agreement between pathologists on the presence of hyperplasia, but some disagreement on the level of atypia.

In long-term Phase III studies (PGL09-026/027 and PGL11-006), the total number of biopsies after 4 treatment courses was 378 and the total number of biopsies 3 months after discontinuation of 4 treatment courses was 380. Excluding PGL09-027 UPA+NETA subjects, the total number of biopsies after 4 treatment courses is 340 and the total number of biopsies 3 months after discontinuation of 4 treatment courses is 318. (see Table 22).

Table 22: Adequate endometrium biopsies after exposure to 2 and 4 treatment courses and 3 months after discontinuation following exposure

Study	PGL09-027		PGL11-006	PGL11-006	UPA total	UPA total w/o NETA
	UPA 10mg + Placebo N=69	UPA 10mg + NETA N=63	UPA 5mg N=230	UPA 10mg N=221		
Biopsy after 6 months administration (2x3 months) (n)	-	-	178	182	360	360
Biopsy after 12 months administration (4x3 months) (n)	47	40	148	145	380	340
Biopsy 3 month after 12 months administration (n)	32	25	144	142	343	318

Source: PGL09-027 CSR Table 14.3.4.1.1 and PGL11-006 CSR Table 14.3.10.1

A summary of biopsy results for all phase 3 studies with ulipristal acetate is presented in Table 23.

Table 23: hyperplasia/malignant neoplasia diagnosed by consensus in adequate biopsies in Phase III studies (PGL07 021 [PEARL I], PGL07 022 [PEARL II], PGL09 026 [PEARL III], PGL09 027 [PEARL III extension], PGL11 024 [Pearl extension 2] and PGL11 006 [PEARL IV])

Study		PGL07-021 Pearl I			PGL07-022 Pearl II			PGL 09-026 Pearl III	PGL 09-027 Pearl III ext.	PGL 11-024 Pearl ext. 2	PGL11-006 Pearl IV	
Doses N=Subjects exposed		Placebo N=48	5 mg N=95	10 mg N=98	Leuprorelin N=101	5 mg N=97	10 mg N=103	10 mg N=209	10 mg (N=131)	10 mg (N=64)	5 mg N=230	10 mg N=221
Adequate biopsies (n) and Cases of any type of hyperplasia or malignant neoplasm (%)												
At screening	n	48	88	95	91	89	100	165	(105)	(50)	219	203
	Hyp	0	1 (caH)	0	0	1 (s)	0	0	-	-	0	0
	ECa	0	0	0	0	0	0	0			0	0
3-month exposure	n	39	78	78	88	86	95	176	-	-	1	-
	Hyp	0	0	0	0	1 (s)	0	0	-	-	1(sa)[b]	-
	ECa	0	0	0	0	0	0	0			-	
3-6 m after 3-month exposure	n	30	60	61	60	58	62	38	-	-	-	-
	Hyp	1 (caH)	0	0	1 (s)	0	0	0	-	-	-	-
	ECa	0	0	0	0	0	0	0				
2 x 3-month exposure	n	-	-	-	-	-	-	-	16[a]	-	178	182
	Hyp	-	-	-	-	-	-	-	0	-	1 (s)	(1s, 1sa)
	ECa								0		1[c]	0
4 x 3-month exposure	n	-	-	-	-	-	-	-	87	-	148[e]	145[e]
	Hyp	-	-	-	-	-	-	-	0	-	1 (caH)	0
	ECa								0		0	0
3 months after 4 x 3-month exposure	n	-	-	-	-	-	-	-	57[d]	-	144	142
	Hyp	-	-	-	-	-	-	-	0	-	1 (c)	0
	ECa								0		0	0
8 x 3-month exposure	n	-	-	-	-	-	-	-	-	42	-	-
	Hyp	-	-	-	-	-	-	-	-	0	-	-
	Eca									0		
3 months after 8 x 3-month exposure	n	-	-	-	-	-	-	-	-	19[d]	-	-
	Hyp	-	-	-	-	-	-	-	-	0	-	-
	Eca									0		

a includes only a subset of subjects, as biopsy was performed if endometrium was thickened > 18mm

b unscheduled visit biopsy

c pre-existing condition

d subset of subjects; biopsy was performed if non-physiological findings were reported by at least one pathologist after 4 courses (Study PGL09-027) or after 8 courses in ongoing Study PGL11-024 (biopsy snapshot-provided in Dec responses.)

Hyp= Hyperplasia, s= simple hyperplasia, sa= simple atypical hyperplasia, c= complex hyperplasia, caH=complex atypical hyperplasia, ECa= endometrial carcinoma.

Dark shaded cells highlight hyperplasia and neoplasm, **bold numbers** indicate cases with nuclear atypia.

Frequency of hyperplasia

Prior to any treatment a prevalence of endometrial hyperplasia of 1.82% was reported in the target population, which is expected considering patients were recruited based on myoma associated with abnormal uterine bleeding (AUB) and the age group of women with symptomatic myoma (i.e. > 50% above 40 years old) and the well-established relationship between both AUB and age with endometrial hyperplasia in pre-menopausal women (Lacey, 2012; Iram, 2010).

During treatment, sporadic cases of endometrial hyperplasia were recorded in all treatment groups, whatever the duration of treatment. Hyperplasia spontaneously occurs in this population demonstrated by one case of atypical hyperplasia in the placebo group and one case of simple hyperplasia following GnRH-agonist treatment.

The frequency was very low and comparable between groups as detailed in Table 24 (0.45% to 2.56%). The frequency of hyperplasia in all short-term and long-term Phase III studies excluding subjects exposed to NETA was calculated using an ITT approach (conservative approach for frequency calculation, whereby a subject is counted only once in the denominator despite providing up to three post treatment biopsies), meaning that the denominator is composed of all subjects with at least one adequate biopsy having been exposed to UPA or comparator whatever the duration of treatment. With this approach, the frequency is 0.89% (7/789) (95% CI 0.36% to 1.82%) for hyperplasia and 0.38% (3/789) (95% CI 0.08% to 1.11%) for hyperplasia with atypia.

Table 24: Frequency of hyperplasia (all types of hyperplasia) and of atypical hyperplasia over all Phase III studies (excluding NETA).

Population and (number of all adequate biopsies taken)	**Frequency of hyperplasia (all)**	**Frequency of atypical hyperplasia**
Target population prior to treatment	9/493 (1.82%)	0/493 (0.00%)
Placebo group	1/39 (2.56%)	1/39 (2.56%)
Leuprolide group	1/88 (1.13%)	0/88 (0.00%)
Ulipristal acetate 5 mg group	5/342 (1.46%)	2/342 (0.58%)
Ulipristal acetate 10 mg group	2/447 (0.45%)	1/447 (0.22%)
Ulipristal acetate both groups	7/789 (0.89%)	3/789 (0.38%)

- Source: PGL07-021, Table 14.3.20 and 14.3.36; PGL07-022 Table 14.2.36 and 14.2.51; PGL09-026 Table 14.3.11.1; PGL09-027, Table 14.3.11.1; PGL11-006, Table 14.3.10.1, PGL11-024 Table 14.3.10.1.

Applying HRT guideline EMEA/CHMP/021/97 Rev.1, the correct calculation of hyperplasia incidence rate for 4 repeated intermittent treatment courses with ulipristal acetate (i.e. an observational period of 18 months) is 0.59% (95% CI 0.07% to 2.12%, NETA subjects excluded). If prevalence at one year overall treatment duration is considered, prevalence rate for hyperplasia and atypical hyperplasia is 0.3% (95% CI 0.01% to 1.64%), i.e. 1 subject with complex atypical hyperplasia at Visit 11 (PGL11-006) out of now 340 biopsies after 4 treatment courses (NETA exposed subjects excluded).

No endometrial carcinoma occurred in this population and consequently the incidence rate for endometrial carcinoma is 0% with a two-sided 95% CI of 0% to 1.09%.

Whichever population is considered, incidence rate over 18 months, prevalence and frequency of hyperplasia with ulipristal acetate are below 1% and the upper level of the respective confidence interval is always below 2.5%.

The calculated prevalence of hyperplasia per number of treatment courses in short-term and long-term studies is presented in Table 25 After two treatment courses, which is currently the approved duration of treatment, hyperplasia was observed in 0.83% of subjects which is in line with the prevalence of hyperplasia in comparator groups, the target population and in published literature. There is no increase of hyperplasia prevalence with repetition of treatment courses.

Table 25: Prevalence of endometrial hyperplasia per number of treatment courses in short-term and long-term Phase III studies (PGL07-021, PGL07-022, PGL09-026/027, PGL11-006 and PGL11-024)

Study	UPA 5mg	UPA 10mg	UPA total	UPA total w/o NETA	Observed cases of hyperplasia	Hyperplasia prevalence (w/o NETA)
Biopsies after 1 course of treatment (n)	165	349	514	430	2	**0.46%**
Biopsies after 2 courses of treatment (n)	178	182	360	360	3	**0.83%**
Biopsies after 4 courses of treatment (n)	148	232	380	340	1	**0.3%**
Biopsy 3 month after 4 courses of treatment (n)	144	199	343	318	1	**0.3%**
Biopsies after 8 courses of treatment (n)	-	42	42	42	0	**0.0%**

In addition the applicant performed a Biopsy Interim Snapshot (cut-off date of 06th November 2014) of the ongoing Study PGL11-024. Study PGL11-024 is an extension study of Study PGL09-026/027 providing up to a total of 8 repeated intermittent treatment courses.

Of the 42 adequate biopsies from the 47 subjects exposed to 8 treatment courses (Visit III), 100% of biopsies had a diagnosis of benign endometrium. Of the 21 subjects who underwent a follow-up biopsy (Visit IV; only if non- adequate biopsy at Visit III or a diagnosis of other than benign physiologic endometrium by at least 1 of the 3 expert pathologists), 19 biopsies were adequate and all (100%) were diagnosed as benign endometrium.

Comparison of the incidence rate with the baseline incidence in healthy women of premenopausal age reported in public literature

The applicant performed a literature research on PubMed, Embase, Google Scholar and Scopus document search. No publication could be identified that provided incidence rates in a premenopausal population. The incidence of hyperplasia in a healthy pre-menopausal population without gynaecological symptoms, is not well established. These women do not routinely undergo endometrial biopsies, curettage or hysterectomies. Incidence rates of hyperplasia were only found for postmenopausal women under hormone replacement therapy. A study including 3006 women with abnormal uterine bleeding, aged from 30 to 50 years, reported that the incidence of hyperplasia increased with increasing age (Iram et al., 2010).

Totally 13 publications were however considered relevant for prevalence rate calculation. The prevalence of endometrial hyperplasia in a premenopausal population in the reviewed publications ranges from 2% to 25.3% with 0.03% to 1.26% for atypical hyperplasia.

For ulipristal acetate prevalence calculation:

Considering prevalence is “a figure for a factor at a single point in time” (Shields, 2003), if prevalence at one year overall treatment duration is considered, prevalence rate for hyperplasia and atypical hyperplasia is 0.3% ((95% CI 0.01% to 1.64%), i.e. 1 subject with complex atypical hyperplasia at Visit 11 (PGL11-006) out of 338 biopsies after 4 treatment courses (PGL09-027 and PGL11-024, NETA exposed subjects excluded).

If calculating the frequency of hyperplasia using the previously explained “ITT approach”, (conservative approach for frequency calculation, whereby a subject is counted only once in the denominator despite providing up to three post treatment biopsies), the frequency of hyperplasia in all Phase III studies (short-term and long-term) excluding subjects exposed to NETA is 0.89% (7/789) (95% CI 0.36% to 1.82%) for hyperplasia and 0.38% (3/789) (95% CI 0.08% to 1.11%) for hyperplasia with atypia. This conservative approach is still well below the reported prevalence in the identified publications.

The hyperplasia incidence after ulipristal acetate treatment and prevalence compares well to published literature. Repetition of ulipristal acetate treatment courses does not increase the occurrence of endometrial findings, i.e. hyperplasia with or without atypia or adenocarcinoma.

Non-Physiological Endometrial Changes (referred as PAEC)

The pathologists were asked to record any non-physiological changes, including PAEC features such as:

- epithelial changes (further classified as secretion, mitoses or apoptotic changes),
- presence of extensive cysts,
- unusual vascular changes (further classified as chicken-wire capillaries, thick-walled vessels or ectatic vessels),
- any other observations.

At screening in Study PGL11-006, in 422 biopsies adequate for review, at least 2 pathologists reported non-physiological changes compatible with PAEC in a total of 34 (8.1%) biopsies.

At Visit 8 (10 to 18 days after the start of menstruation following treatment course 2), in biopsies adequate for review from 360 subjects, at least 2 pathologists reported non-physiological changes in a total of 64 (17.8%) biopsies, 29 (16.3%) biopsies from the 5 mg/day group and 35 (19.2%) biopsies from the 10 mg/day group.

In the PGL11-006 Part II interim analysis, for Visit 11, in 122 biopsies adequate for review, at least 2 pathologists reported non-physiological changes in a total of 25 (20.5%) biopsies, 17 (24.6%) biopsies from the PGL4001 5 mg group and 8 (15.1%) biopsies from the PGL4001 10 mg group.

For Visit 12, in 39 biopsies adequate for review, at least 2 pathologists reported non-physiological changes in a total of 4 (10.3%) biopsies, 2 (8.7%) biopsies from the PGL4001 5 mg group and 2 (12.5%) biopsies from the PGL4001 10 mg group.

In the ulipristal acetate Phase III studies, non-physiological features were shown to occur at baseline prior to any exposure to ulipristal acetate in 2 to 14 % (if taken the evaluation of at least 2 out of 3 pathologists). When biopsies were taken under treatment, these non-physiological changes were seen in approximately 60% of biopsies (Studies PGL07-021 and PGL07-022). After only one menstrual bleed, the frequency of non-physiological features decreased to below 30% (Study PGL09-026). Within 3 to 6 months after end of treatment (Part B Studies PGL07-021 and PGL07-022, and Study PGL09-026) they decreased to baseline frequency.

Repeated intermittent 3-month courses of ulipristal acetate did not increase the occurrence of PAEC (Studies PGL09-027 and PGL11-006). The frequency of non-physiological changes after four 3- month treatment courses was lower to the frequency observed after two treatment courses (Visit 8; 16.3% and 19.2% for the 5 mg and 10 mg group respectively) see Table below. After a follow-up period of approximately 3 months after the end of the four treatment courses, the occurrence of non-physiological changes was comparable to screening values with 9.3% and 6.1% for the 5 mg and 10 mg respectively.

Table 26: Endometrium biopsy non-physiological descriptions where diagnoses of 2 or 3 pathologists were in agreement (Studies PGL09-027, PGL11-006 2nd Biopsies Interim analysis – November 2014)

		Study PGL09-027		**Study PGL11-006**	
		10 mg UPA + Placebo (N=69)	**10 mg UPA + NETA (N=63)**	**Ulipristal acetate**	
				5 mg (N=230)	**10 mg (N=221)**
	Non-physiological	**4 (7.1%)**	**7 (14.3%)**	**17 (7.8%)**	**17 (8.4%)**

Screening	*Epithelial changes*	*4 (7.1%)*	*7 (14.3%)*	*14 (6.4%)*	*17 (8.4%)*
	Extensive cyst formation	*0*	*0*	*3 (1.4%)*	*1 (0.5%)*
	Unusual vascular changes	*0*	*2 (4.1%)*	*3 (1.4%)*	*1 (0.5%)*
After 1 treatment course*	**Non-physiological**	**20 (30.8%)**	**15 (26.3%)**	-	-
	Epithelial changes	*19 (29.2%)*	*14 (24.6%)*	-	-
	Extensive cyst formation	*9 (13. 8%)*	*2 (3.5%)*	-	-
	Unusual vascular changes	*5 (7. %7)*	*8 (14.0%)*	-	-
After 2 treatment course**	**Non-physiological**	-	-	**29 (16.3%)**	**35 (19.2%)**
	Epithelial changes	-	-	*27 (15.2%)*	*31 (17.0%)*
	Extensive cyst formation	-	-	*5 (2.8%)*	*5 (2.7%)*
	Unusual vascular changes	-	-	*2 (1.1%)*	*3 (1.6%)*
After 4 treatment course***	**Non-physiological**	**11 (23.4%)**	**11 (27.5%)**	**24 (16.3%)**	**15 (10.4%)**
	Epithelial changes	*9 (19.1%)*	*10 (25.0%)*	24 (16.3%)	15 (10.4%)
	Extensive cyst formation	*3 (6.4%)*	*1 (2.5%)*	5 (3.4%)	4 (2.8%)
	Unusual vascular changes	*5 (10.6%)*	*8 (20.0%)*	1 (0.7%)	1 (0.7%)
Follow-up ****	**Non-physiological**	-	-	**13 (9.3%)**	**8 (6.1%)**
	Epithelial changes	-	-	12 (8.6%)	8 (6.1%)
	Extensive cyst formation	-	-	1 (0.7%)	1 (0.8%)
	Unusual vascular changes	-	-	1 (0.7%)	0

Return to menstruation

Menstruation returned quickly after end of treatment in both treatment groups in Study PGL11-006 (Part I). Following treatment course 1, the mean (median) time to return of menstruation for subjects in the PGL4001 5 mg and 10 mg groups was 24.7 (23.0) and 27.7 (27.0) days, respectively. Following treatment course 2, the mean (median) time to return of menstruation for subjects in the PGL4001 5 mg and 10 mg groups was 28.2 (26.0) and 30.5 (28.0) days, respectively. Six subjects had not returned to menstruation 90 days after end of treatment, which as per protocol led to their withdrawal. Following discontinuation of treatment course 3, the mean (median) time to return of menstruation for the 186 subjects in the PGL4001 5 mg group was 29.1 (27.0) days, and for the 180 subjects in the PGL4001 10 mg group the mean (median) was 30.8 (28.5) days. Following treatment course 4, the mean (median) time to return of menstruation for the 174 subjects in the PGL4001 5 mg group was 28.5 (27.0) days, and for the 168 subjects in the PGL4001 10 mg group the mean (median) was 32.7 (29.0) days.

In all the short-term and long-term Phase III studies the majority of subjects returned to menstruation quickly after the end of treatment(s) with ulipristal acetate. The mean duration was 27-34 days in short-term, 24.9-33.2 days in long-term Study PGL09-026/027 in placebo group after treatment course 4.

Serious adverse event / deaths / other significant events

During the study, 16 (3.5%) subjects reported 18 on-treatment SAEs, 2 of which were considered treatment related, and 13 (2.9%) subjects reported 16 off-treatment SAEs, 11 of which were considered PGL4001-related. The most commonly reported SAE was menorrhagia, reported for 6 subjects, of which one was considered unrelated to PGL4001 (considered an AESI), and 4 subjects had the SAE of uterine leiomyoma reported, (2 reports of “myoma in status nascendi”, 1 report of “partial expulsion of uterine myoma” and 1 report of “necrosis of myoma node”), all considered PGL4001-related.

Eleven treatment emergent AESI were reported for 11 (2.4%) subjects, 9 of which were non-serious and included: 4 reports of endometrial hyperplasia which were diagnosed following curettage to treat the SAE of menorrhagia (all 4 reports for subjects from the PGL4001 5 mg group); 2 reports of menorrhagia; 1 report of endometrial hypertrophy; and 2 reports of clinical laboratory abnormalities (one of increased alkaline phosphatase and one of liver function test abnormalities without evidence of liver function impairment). One SAE/AESI of endometrial cancer was reported, but there is evidence that this was a pre-existing condition.

In the on-going study PGL11-024, one SAE was reported until the 31 May 2014 cut-off date. "Crossed fused right renal ectopia" (PT: ectopic kidney) was reported for a child exposed to ulipristal acetate 10 mg once daily in utero for approximately one month. The investigator assessed the event to be unrelated to ulipristal acetate treatment. The role of concomitant drugs used by mother at the beginning of first trimester like domperidone and tetrazepam could not be excluded. The incidence of ectopic kidney reported in the literature is 1:7000 (Narci A et al, 2010).

No deaths were reported during treatment with ulipristal acetate in any completed studies.

Two deaths were reported in the ongoing study PGL11-006 Part II: one due to murder and the other was an accidental death; none of them considered by Investigators as related to the study treatment.

Laboratory findings

The mean (median) Hb value at screening was 12.27 (12.50) g/dL (Safety Set, normal range 11.5 to 15.5 g/dL); 12.26 (12.55) g/dL for subjects from the PGL4001 5 mg group and 12.29 (12.40) g/dL for subjects from the PGL4001 10 mg group. At visits 3 to 10, Hb levels were increased compared to screening values, reaching a peak at visit 10 (end of treatment course 4), with mean (median) levels of 13.16 (13.20) g/dL (Safety Set overall); levels for the PGL4001 5 mg and 10 mg groups were 13.02 (13.10) g/dL and 13.31 (13.35) g/dL, respectively. At visit 12 end of study follow-up, the mean (median) Hb value was 12.90 (13.10) g/dL (Safety Set).

As expected, the number of subjects with Hb levels less than lower limit of normal (<LLN) decreased during the study, with a total of 32 (7.9%) subjects with levels <LLN at visit 7 (end of treatment course 2), and 26 (7.7%) subjects with levels <LLN at visit 10 (end of treatment course 4), compared to 115 (26.1%) subjects at visit 2, the start of treatment course 1.

At visit 2 (prior to receiving treatment at the start of treatment course 1), 164 (72.9%) subjects from the PGL4001 5 mg group and 162 (75.0%) subjects from the PGL4001 10 mg group had Hb levels within the normal range. At visit 10, 152 (89.9%) and 159 (94.6%) subjects from the PGL4001 5 mg and 10 mg groups, respectively, had Hb levels within the normal range.

The mean Hct value at screening was 0.40. Hct levels increased from screening to reach a peak of 0.42 at Visit 7 and visit 10. Similarly, the number of subject with Hct levels <LLN decreased at each successive study visit.

The mean (median) values for both AST (normal range 0 to 37 U/L) and ALT (normal range 0 to 47 U/L) from screening and throughout the study did not vary greatly, with little difference between the PGL4001 5 mg and 10 mg groups.

At screening and visit 2 (prior to treatment administration at the start of treatment course 1), 11 (2.5%) subjects presented high AST values at both visits, and 6 (1.3%) and 7 (1.6%) subjects presented high ALT values at these visits (Table 52). At visit 5 (during the last 8 days of treatment course 1), the numbers of high values (>ULN) observed were 17 (4.0%) and 18 (4.2%) subjects for AST and ALT, respectively. At subsequent visits up to visit 12, the number of subjects with high values (>ULN) of AST ranged between 4 subjects at visits 6 and 9, and 10 (2.5%) subjects at visit 7. The number of subjects with high values (>ULN) of ALT ranged between 2 subjects at visit 9 and 7 (2.0%) subjects at visit 10. Shift tables describing the changes to numbers of AST/ALT values with respect to the normal range observed during the study for the overall Safety Set are provided in Section 14.1.6, Table 14.3.16.

Lipids were measured at screening and Visits 7, 10 and 12. At Visit 7, the mean levels of total cholesterol were slightly higher compared with at screening. A total of 185 (41.4%) subjects had total cholesterol levels >ULN at screening; at visits 7, 10 and 12, the corresponding figures were 221 (54.3%), 206 (60.1%) and

177(52.7%) subjects, respectively, with total cholesterol levels >ULN. Levels of triglycerides increased slightly during the study. At screening a total of 57 (12.8%) subjects had levels of triglycerides which were >ULN, corresponding numbers at visits 7, 10 and 12 were 81 (19.9%), 67 (19.5%) and 53 (15.8%) subjects.

The majority of subjects maintained normal levels of triglycerides and HDL, and high levels of LDL from baseline to Visit 7. The ratio of total cholesterol / HDL cholesterol was evaluated (post-hoc analysis). The ratio of total cholesterol / HDL cholesterol was always <4. At screening, the mean ratio of total cholesterol / HDL cholesterol was 3.30 and 3.38 for subjects in the 5 mg/day and 10 mg/day groups, respectively, and at Visit 7 corresponding ratios were 3.44 and 3.44, respectively.

No trends for changes in other biochemistry parameters were observed.

Coagulation parameters were measured at screening. Only 1 subject had an on-treatment out of normal range value. This subject had a high APTT value one month in treatment course 1 at a repeated screening test (i.e. 42.1 seconds; normal range 27.0 to 40.0 seconds), but prothrombin time and INR were within normal ranges.

Blood glucose levels were not routinely measured in this study, but no TEAEs of change in glucose levels or glucose metabolism were reported.

Measurement of estradiol (E2), FSH and thyroid stimulating hormone (TSH) was performed at screening and for E2 at visit 7. There were no identifiable trends in estradiol levels and very few on-treatment values of E2 outside the normal range. Increases in E2 levels of clinical relevance (normal range of E2, 0 to 399 pg/mL) at visit 7 were seen for a total of 7 subjects from the PGL4001 group and 3 subjects from the PGL4001 10 mg group, and at visit 10 were seen for 4 subjects from the PGL4001 5 mg group and 1 subject from the PGL4001 10 mg group.

Increases in E2 levels of clinical relevance were seen for a total of 7 subjects in the 5 mg/day group and 3 subjects in the 10 mg group at Visit 7 (end of treatment course 2). There was no evidence that levels of E2 decreased during the study; in general levels remained constant for most individuals during the study.

Effect of ulipristal acetate on the pituitary-ovary axis during treatment in clinical studies

The MAH provided additional data on endocrine parameters in order to evaluate the effect of ulipristal acetate on the pituitary-ovary axis during treatment in clinical studies. Endocrine parameters were measured at pre-defined time points during all clinical studies. Daily administration of ulipristal acetate partially suppressed FSH. Oestrogen levels (E2) tended to be in the mid-follicular range during treatment. Progesterone levels (P4) were reduced during treatment, and there was no effect on prolactin.

In the two Phase II studies PGL-N-0287 and PGL-N-0090 in the target population, subjects were treated for 3 months with 10 mg and 20 mg of ulipristal acetate. Measurement of prolactin, luteinising hormone (LH), FSH, E2 was performed approximately every 14 days. No effect on FSH or LH levels was observed. In addition, there was no indication of any ulipristal acetate mediated effects on prolactin and E2.

In the Phase II Study PGL-H-510, healthy subjects were treated for 3 months with 2.5 mg, 5 mg and 10 mg of ulipristal acetate. Endocrine assessments showed no appreciable variation between groups at baseline and after 3 months of treatment. P4 was measured at lower values (< 3 ng/mL) during treatment in 82% or 80% of subjects treated with ulipristal acetate 5 or 10 mg respectively compared to placebo (0%), indicating absence of ovulation.

In short-term Phase III Study PGL07-021, median E2 levels were increased towards baseline in all groups (ulipristal acetate 5 mg, 10 mg and placebo) as the baseline value was taken during menstruation, when levels are at its lowest. Differences under treatment were observed due to placebo subjects continuing to experience normal menstrual cycles and most ulipristal acetate treated subjects being in anovulation. In all

groups, however E2 concentrations remained at follicular phase levels. After the end of treatment with ulipristal acetate, median E2 values increased with ulipristal acetate, indicating that full ovarian function resumes promptly within a few weeks of treatment end.

P4 levels were similar across treatment groups (ulipristal acetate 5 and 10 mg and placebo) at baseline and Week 5, but at Weeks 9 and 13 they were significantly lower with ulipristal acetate than with placebo. The majority of subjects in ulipristal acetate treatment groups had constantly low values whilst under treatment indicating absence of ovulation, although maximum values close to or above 5.0 ng/mL in all groups indicating a persistence of ovulation in some subjects. After treatment, at Week 17, the mean progesterone levels increased in the ulipristal acetate groups, suggesting resumption of ovulation. Results with ulipristal acetate in short-term Phase III studies PGL07-021 PGL07-022 were comparable.

In the two long-term Phase III studies PGL09-026/027 and PGL11-006, no decrease of E2 levels compared to baseline was observed after repeated treatment courses. E2 levels were controlled and remained stable at a mid-follicular phase level. Levels obtained after 4 treatment courses did not differ from values obtained after one treatment course.

Effects of Esmya on oestrogen levels and bone mineral density

It is established that low oestradiol levels are associated with bone mineral density loss, and decreased oestradiol levels were identified as a major risk factor in the Framingham Study (Hannan et al., 2000). The association of anovulation and bone mineral density loss in women is on the contrary not established as anovulation is not mandatorily associated with low oestrogen levels. Typically patients with a polycystic ovarian symptom have anovulatory cycles but no decrease in bone mineral density as they maintain significant oestrogen levels (Kassanos et al., 2010). Thus oestrogen levels are essentially the determinant for bone mineral density loss and it is established that a level of oestradiol above 30 pg/mL is sufficient for maintaining adequate bone mineral density (Barbieri, 1998).

The oestradiol levels recorded before, during treatment and after treatment in short-term and long-term studies with ulipristal acetate. In the short-term Phase III study PGL07-022, no impact on bone markers was observed following 3-month treatment with ulipristal acetate whereas a negative impact of the GnRH-agonist on bone markers was demonstrated ($p<0.001$; Study PGL07-022). With GnRH-agonist, oestradiol levels were reduced importantly and mean levels were below the postmenopausal threshold of 30 pg/mL.

As no effect was seen on urinary or serum bone markers after 3-month treatment with ulipristal acetate and owing to the fact that in absence of a comparator arm (either placebo or active comparator) in the long-term Phase III studies (PGL09-026/027 and PGL11-006) any change in bone marker measurements or bone mineral density would be difficult to interpret, the absence of impact on bone mineral density was assessed and confirmed in the above mentioned long-term trials by documenting the maintenance of serum oestradiol levels. Results are presented above.

In addition, endometrium thickness is directly influenced by oestrogen levels and could therefore be considered as an indicator of premenopausal oestrogen levels. Endometrium thickness range is rather variable during a physiological ovulatory cycle in premenopausal women, but an endometrial thickness < 5 mm indicates low oestradiol levels as seen in postmenopausal women (Breijer et al., 2012).

Women treated with ulipristal acetate do not have a decreased endometrial thickness. In short-term Phase III studies, the percentage of subjects with an endometrial thickness < 4 mm remains in the range from 8.7% to 19.3% which is comparable to screening and to the placebo control group (range 9.9%-20.0%). In long-term Phase III Studies PGL09-026/027 and PGL11-006, the repetition of treatment courses did not increase the percentage of patients with thin endometrium in comparison to pre-treatment or the placebo control group of Study PGL07-021

Discontinuation due to adverse events

Overall, 32 subjects, 16 in the PGL4001 5 mg group and 16 in the PGL4001 10 mg group, discontinued the study early due to safety reasons related to PGL4001.

In general, the withdrawals due to TEAEs considered PGL4001-related were for a variety of reasons with few TEAEs occurring in more than one subject; 5 subjects withdrew due to SAEs considered related to PGL4001. Three subjects, one from the PGL4001 5 mg group and 2 from the PGL4001 10 mg group, were withdrawn due to the SAE of uterine leiomyoma, all considered PGL4001-related. These included one subject who experienced "partial expulsion of myoma" (PT: uterine leiomyoma), and 2 subjects who experienced a "myoma in status nascendi" (PT: uterine leiomyoma). One subject withdrew following treatment course 4 due to the SAE of endometriosis, and one subject due to the SAE of bipolar disorder, both were considered PGL4001-related.

PGL4001-related TEAEs leading to study withdrawal included 2 subjects who withdrew due to hypertension and 1 subject due to blood pressure increase. In addition, 3 reports of headache, 2 reports of nausea and dizziness, and single reports of anxiety, hypersensitivity, obesity, dyspnoea, abdominal discomfort/pain/distension, depression, diplopia, balance disorder, coordination abnormal, generalised rash, hyperhidrosis, urticaria, breast pain, menorrhagia, hot flush and malaise were reported as PGL4001-related TEAEs leading to subject withdrawal.

In addition, 3 subjects requested to discontinue the study following AEs or changes to laboratory parameters. Subject 472/08 (PGL4001 5 mg group) had an SAE of menorrhagia that was considered PGL4001-related by the Investigator; she continued in the study but subsequently requested to withdraw due to 'heavy bleeding during menses'. Two subjects requested to withdraw from the study with the reasons provided as 'elevated liver enzymes' and 'elevated laboratory results'.

Special population

Pregnancies

- During or after treatment in clinical studies

During all clinical studies, subjects were requested to use a non-hormonal contraception and the objectives of clinical studies with ulipristal acetate in women with symptomatic uterine fibroids did not include fertility parameter assessment upon cessation of treatment. As 11 December 2014, in more than 1000 subjects treated in clinical studies with ulipristal acetate for fibroids, 8 pregnancies after treatment were reported (0.7%). No conception was reported under treatment with ulipristal acetate.

Three cases of pregnancy post-treatment have been reported in short-term studies with fibroid subjects (PGL07-021 and PGL07-022), with conception time between 2-5 months after the last treatment dose.

In the ongoing Phase III long-term clinical studies in the target population, 5 pregnancy reports have been received, one in Study PGL11-024 (drug exposure during pregnancy), with conception time during an off-treatment period few weeks before start of treatment course 1 and four other pregnancy reports were received from the ongoing Part II of Study PGL11-006.

- During or after treatment in post-marketing

Esmya post-marketing data contain some reports of pregnancy associated with ulipristal acetate treatment in women with symptomatic uterine fibroids. As of December 2014, an estimate of > 110,000 patients were treated with ulipristal acetate for fibroids. 60 pregnancy reports were received (47 with drug exposure before pregnancy i.e. conception occurred after treatment, 12 with drug exposure during pregnancy and one report with unspecified exposure timing). Not all outcomes are known at the time of writing.

In 11 out of 47 cases of drug exposure before pregnancy, the pregnancy ended with spontaneous, missed or induced abortion. In 3 out of 12 cases of drug exposure during pregnancy and in the pregnancy with drug exposure timing unspecified, the pregnancy ended with spontaneous, missed or induced abortion.

The reported spontaneous abortion rates are not unexpected with regards to the target population.

- After treatment in literature

A search of the published literature dated 2nd December 2014 retrieved some pregnancy case reports after ulipristal acetate treatment in women with symptomatic uterine fibroids.

One publication (Luyckx M et al, 2014) describes a first series of 18 pregnancies in 21 patients attempting to get pregnant after treatment with ulipristal acetate for symptomatic uterine fibroids. This was a retrospective analysis of patients included in studies PGL07-022 and PGL09-026 followed beyond the study end in one study centre. Overall, 15 patients succeeded (71 %) to get pregnant, totalling 18 pregnancies.

The literature search also retrieved a case report (Monleon J et al, 2014) describing pre- treatment with ulipristal acetate 5 mg prior to pregnancy in a 37-year old woman (gravida 1, abortus 1), with a history of intramural uterine fibroids and prior myomectomy. A normal endometrial morphology cavity was observed following treatment with ulipristal acetate. Three months after the end of ulipristal acetate treatment, the patient was found to be 5 weeks pregnant.

Also, of interest, another case report (Wdowiak A, 2013) was retrieved describing the case of a 35-year old patient with intramural uterine fibroids admitted for continued infertility treatment receiving a 3-month course of Esmya prior to intracytoplasmic sperm injection. The patient conceived, the pregnancy went to term and delivered following spontaneous labour a healthy baby (Wdowiak A, 2014).

Post marketing experience

The applicant estimates that approximately 60 500 women have been treated with Esmya as of 22 February 2014, based on cumulative sales figures. Of those, 1,386 have been enrolled in the non-interventional PregLem-sponsored Post-Authorisation Safety Study (PASS) PREMYA (PGL10-014).

The latest PSUR (EMEA/H/C/002041/PSUV/0025, covering the period 23 August 2013 to 22 February 2014) included these data. During the PSUR interval no new safety issues have been identified from clinical trials, post-marketing reports or literature. The identified and potential risks were considered adequately covered in the RMP and there was no need for an update of the product information.

2.6.1. Discussion on clinical safety

The current variation application for Esmya is intended to extend the current, short-term pre-operative treatment to repeated intermittent treatment. In completed studies, 1,053 women have been exposed to ulipristal acetate for ≥3 months to the target dose of 5 mg/day or higher. Of these, 541 patients were exposed for ≥ two 3-month treatment courses and 457 subjects were exposed to four 3-month treatment courses, including results from the study PGL11-006 (Part I). In Part II of the ongoing Study PG11-006, 381 subjects have completed 3 courses of treatment of whom 354 subjects have also completed a 4th course of treatment. Thus, the number of subjects exposed to ulipristal acetate for up to 6 months is large (above 6000), whereas the numbers of subjects exposed ≥6 months and ≥12 months, respectively, are still not huge and just above the ICH E1 requirements for long-term exposure.

The demographic characteristics were similar across the phase 3 studies, including the most recent study PGL11-006. The studies included mainly white females, aged just above 40 years, with a mean BMI slightly above 25 and the majority were of child-bearing potential.

In Study PGL11-006 Part I, the most common TEAEs were headache, and hot flush. Other common TEAEs were influenza, breast pain/tenderness/discomfort, nausea, nasopharyngitis, fatigue and pelvic pain. The proportion of subjects reporting on-treatment TEAEs was higher during the first treatment course (44%) than during the second treatment course (<30%). A similar pattern was seen for treatment–related adverse events, i.e. a higher frequency reported during the first treatment course than during the second treatment course, and with hot flush and headache being most frequently reported. There were no obvious dose-related AEs.

Off-treatment TEAEs (from >7 days after the last dose of a treatment course to the beginning of the next) were mainly related to uterine bleeding, e.g. dysmenorrhoea and menorrhagia. Fewer off-treatment TEAEs were reported following treatment course 2 than treatment course 1.

Concerning adverse events of special interest (reproductive and breast disorders, excessive uterine bleeding, hot flushes and other castration-related symptoms, ovarian cysts, dysmenorrhea, headache and gastrointestinal disorders) the data from Study PGL11-006 are in line with previous results and do not give any cause for concern.

The endometrial safety of ulipristal acetate, in particular endometrial thickness, hyperplasia/carcinoma and non-physiological changes, has been extensively discussed during the initial marketing authorisation procedure EMEA/H/C/2041, the variation EMEA/H/C/2041/II/19 extending the indication to two treatment courses and the present application .

Due to the mechanism of action of ulipristal acetate, thickening of the endometrium is expected, as observed in previous short-term and long-term studies. The endometrial thickness has shown a similar pattern across studies, with about 5% showing an endometrial thickness >16 mm at screening and 7-15% of subjects showing a thickness >16 mm at 10-18 days after start of menses following treatment course 1. In study PGL11-006, the median endometrium thickness was similar to screening levels at all time-points during the study and post-treatment follow-up. There were fewer subjects with endometrium thickness >16 mm after successive treatment courses (4.9% and 3.5% of patients by the end of second and fourth treatment course, respectively). With regards to endometrial thickness, no significant differences were observed between the PGL4001 5 mg and 10 mg groups.

Considering the available safety information, the applicant was requested to provide further advice in the SmPC for the prescriber on follow-up of patients during long-term treatment with Esmya and how to manage patients with increased endometrial thickness or with altered and/or unexpected bleeding patterns.

Reversible increase in thickness of the endometrium may occur under treatment. In case of repeated intermittent treatment, periodic monitoring of the endometrium is recommended. This includes annual ultrasound to be performed after resumption of menstruation during off-treatment period. If endometrial thickening is noted, which persists after return of menstruations during off-treatment periods or beyond 3 months following the end of treatment courses, investigation including endometrial biopsy should be performed in order to exclude other underlying conditions, including endometrial malignancy. Similarly, if during repeated intermittent treatment, after the initial reduction in bleeding or amenorrhoea, in case of an altered persistent or unexpected bleeding pattern, such as inter-menstrual bleeding, investigation of the endometrium including endometrial biopsy should be performed in order to exclude other underlying conditions, including endometrial malignancy (see SmPC section 4.4).

Progesterone receptor modulator Associated Endometrial Changes (PAEC) describes the non-physiological histological changes in the endometrium that have been associated with treatment with progesterone receptor modulators. In all specimens of PAEC, there is an inactive, flattened and atrophic appearance of the epithelium. It is thinner than in the normal proliferative menstrual phase, and there is little evidence of mitosis. Repeated intermittent 3-month courses of ulipristal acetate in the 2 long term Phase III studies (PGL09-027 and PGL11-006) did not increase the occurrence of PAEC. From the study results there is no

evidence that appearance of PAEC is a precursor to or a risk factor for more serious conditions of the endometrium such as hyperplasia with atypia or endometrial carcinoma. Repetition of treatment courses did not increase PAEC appearance, frequency or reversibility. Even after exposure to 8 treatment courses the detailed descriptions of PAEC features compare to those after a single treatment course. Overall, the data from this study confirmed a rapid reversibility of SPRM-associated non-physiological endometrial changes following completion of treatment and subsequent menstruation.

With regards to hyperplasia, the MAH has provided an in depth discussion with respect to the characteristics of endometrial hyperplasia and mechanism of action of ulipristal acetate on the endometrium concluding that its impact on the endometrium is specific and different from an unopposed oestrogen effect. In addition, in a previous procedure (EMEA/H/C/2041/II/14) including non-clinical carcinogenicity studies, the CHMP has previously concluded that UPA is not carcinogenic in experimental animals at sufficiently large exposure margins compared to human exposure. Thus, from a mechanistic point of view, it can be agreed that the risk of endometrial hyperplasia and cancer may be lower compared to a continuous oestrogen effect. As in previous studies, endometrium biopsies were obtained at several time points in study PGL11-006. In total in long-term Phase III studies (PGL09-026/027 and PGL11-006), the applicant provided results from 380 biopsies taken 3 months after discontinuation of 4 treatment cycles with ulipristal acetate. With respect to the biopsy results in the clinical studies, the frequency of hyperplasia in all phase 3 studies was low (0.89%) and, importantly, lower than the incidence in study population prior to treatment (1.82%). When looking at the incidence after 4 courses in study 006, the incidence was 0.59% with 5 out of 6 cases being reversible. Preliminary results from the ongoing Pearl extension 2 (8 treatment courses) have not shown any cases of hyperplasia, albeit in a small sample size

No particular pathologic pattern could be identified for the 6 cases of hyperplasia (e.g. progress from simple to complex atypical hyperplasia). In the 3 cases with atypical hyperplasia, one case resolved after having undergone curettage (at which the atypia had been diagnosed), one case spontaneously resolved while receiving ulipristal acetate treatment and one spontaneoulsy resolved within 3 months following treatment end.

Overall, the available data on hyperplasia/malignant neoplasia during ulipristal acetate treatment in clinical trials indicate spontaneous reversibility of hyperplasia. In addition, the incidence of hyperplasia did not increase during subsequent treatment courses.

The incidence of hyperplasia in a healthy pre-menopausal population with no gynaecological symptoms is not well established. However, it is agreed with the applicant that the population with no gynaecological symptom is not the population of patients who will be treated by Esmya. Patients treated with UPA have fibroids with abnormal uterine bleeding (AUB) and other gynaecological symptoms. The Applicant performed literature research where 13 publications were considered relevant for prevalence rate calculation. The prevalence of endometrial hyperplasia in the premenopausal population, reported in the literature, ranges from 2% to 25.8% with 0.03% to 1.26% for atypical hyperplasia. The incidence of hyperplasia in a study including 3006 women increases with age from 1.97% for women 30-40y to 4.68% in the age of 45-50 years (Iram, 2010). The majority of patients treated with UPA for fibroids-related AUB are likely to be > 40 years old. In study PGL11-006 the participants had a mean age around 42 years. In ulipristal acetate phase III studies the prevalence and incidence of endometrial hyperplasia rate were below 1% (0.59%, 95% CI 0.07% to 2.12% over an 18 months period) and comparable with the published literature. Overall, repeated treatment with ulipristal acetate courses does not seem to increase the occurrence of more serious conditions of the endometrium such as hyperplasia with atypia or endometrial carcinoma.

One important issue is that endometrial hyperplasia in most cases is asymptomatic and therefore may go undetected for quite some time. If hyperplasia persists, the condition will evolve and after an asymptomatic time interval becomes symptomatic and initiate further investigation (Archer, 1991). The actual risk of a one-time diagnosis of endometrial hyperplasia will therefore to some part be depending on if the woman is

asymptomatic or symptomatic, and characteristics of symptoms at the diagnosis. When a diagnosis of endometrial hyperplasia is established a spontaneous normalization or a subsequent diagnosis of adenocarcinoma (AC) is possible (Kurman, 1985; Lacey, 2008; Lacey, 2010). When there is no atypia, a quite long delay between the initial diagnosis of hyperplasia and a later diagnosis of AC is reported (11 years -4.1 years). Atypical hyperplasia may indeed develop to adenocarcinoma and a delay in diagnosis may result in a worsened prognosis. However, the incidence of atypial hyperplasia was very low and most likely not higher compared to what could be expected in the background population.

In conclusion, the risk of endometrial hyperplasia associated with the use of UPA is considered as low. However there is limited information available on the long-term effect of Esmya after long-term use as long term treatment has been studied up to 4 intermittent treatment courses only. “Long-term effects of prolonged treatment of the endometrium (including possible malignant changes)” is included as a safety concern in the RMP under missing information (see RMP). Additional long term safety data, although mainly descriptive data, will be collected in the post-authorisation safety study (PGL14-001) following 1500 patients who intend a long-term treatment with UPA for up to 5 years. One of the limitations of PGL14-001 study is that there is no pre-defined number of biopsies because standard gynaecological practice does not recommend endometrial biopsies in asymptomatic patients. Further data on endometrial safety in the context of long-term use of ulipristal acetate will be also available from the ongoing PGL11-024 (Pearl extension 2) which will provide endometrial biopsies after 8 repeated intermittent treatment courses with 10 mg of ulipristal acetate (twice the marketed dose) (see RMP).

An investigation of the observed cases of hyperplasia in Study PGL11-006 and an adequate description of follow-up was provided and showed that there was generally a good agreement between pathologists on the presence of hyperplasia, but some disagreement on the level of atypia. The need for further guidance for pathologists in diagnosing between benign/malignant endometrial biopsy taken during treatment with ulipristal acetate was discussed by the Applicant since even specialist pathologists had difficulties in interpretation of atypia findings.

The discrepancy in diagnosing endometrial hyperplasia (with the current WHO classification which is recommended by FDA and was used for assessment in Phase III studies) is a well-described fact and not specific to the follow-up of treatment with ulipristal acetate. The applicant stated that EU pathologists have been and are extensively trained on PAEC. Since repetition of treatment courses does not lead to an increase in premalignant or malignant diagnoses or in any new features of the endometrium compared to short-term treatment, it is believed that no further training would allow minimising risk of discrepancies between pathologists. The SmPC already contains information about endometrial changes (see SmPC section 4.4) in particular that histological changes denoted as “Progesterone Receptor Modulator Associated Endometrial Changes” (PAEC) should not be mistaken for endometrial hyperplasia. As simple hyperplasia is the principal differential diagnosis to PAEC and simple and complex hyperplasia can occur spontaneously in women of reproductive age with abnormal bleeding and sometimes resolves, the applicant proposed to provide further guidance to the physician on how to proceed in case of any incidental hyperplasia diagnosis. Owing to the fact that compared to simple hyperplasia, only hyperplasia with nuclear atypia is at higher risk of progression to malignancy (Kurman et al. 1985), a different proceeding for atypical and non-atypical hyperplasia is recommended. In case of hyperplasia (without atypia), monitoring as per usual clinical practice (e.g. a follow-up control 3 months later) is recommended. In case of atypical hyperplasia, investigation and management as per usual clinical practice should be performed (see SmPC section 4.4).

Information on the number of cases of hyperplasia observed in the clinical programme, its reversibility, the incidence, and comparison to prevalence in symptomatic menopausal women have been adequately reflected in the SmPC.

Women who get symptomatic relief (less bloating & discomfort due to reduced fibroid size and better energy due to less heavy bleeding) might be inclined to use Esmya persistently without a break. This type of use

poses a risk since intermittent use allows/induces a type of withdrawal bleed, which should offset any developing endometrial hyperplasia. In order to minimise the risk of occurrence of persistent use beyond 3 months, stringent risk minimisation activities were and are undertaken. The proposed SmPC indicates at several occasions that the treatment should not be longer than 3 months continuously as the risk on endometrium is unknown if continued longer and that it must be intermittent in case of the proposed repeated intermittent use (see SmPC sections 4.2, 4.4). Educational material has been sent to all gynaecologists at time of national launches to increase awareness that each Esmya treatment course should be limited to 3 months. From the presented post marketing data the risk seems limited with a low number of cases and no detrimental reported adverse events.

With regards to the effect of Esmya on short-term fertility and long-term fertility, it is noted that fertility is likely to be very low considering the target population's age, fibroid condition and ulipristal acetate's impact on the pituitary-ovary axis. In study PGL11-006 the participants had a mean age around 42 years. From the provided data on fertility from clinical studies and post-marketing data, the treatment with ulipristal acetate does not seem to have a negative impact on fertility either after short-term or repeated intermittent treatment. The need for contraception during treatment is already addressed in the SmPC (see SmPC section 4.4). During the off-treatment interval ovulation resumes rapidly and consequently pregnancies may occur if no contraception is used. The Esmya SmPC already describes the pregnancy prevention prior treatment. In addition, a pregnancy test is indicated prior to treatment start in case of a suspected pregnancy (see SmPC section 4.4)

The effects of Esmya on oestrogen levels and bone mineral density were discussed by the applicant. The majority of women treated with ulipristal acetate were anovulatory, though their E2 levels remained generally in physiological ranges after 3 months of treatment (Study PGL-H-510). Bone turnover was assessed by measurement of bone markers in Study PGL07-022, and by bone density scans in Study PGL-N-0090. The active control in study PGL07-022 was leuprorelin. The biochemical markers of bone resorption showed higher values with leuprorelin treatment compared to treatment with ulipristal acetate after 3 months. In study PGL-N-0090, there was no evidence of any change to bone density after 6 months of treatment with ulipristal acetate. It is likely that no adverse influence on bone mineral density is to be expected with repeated treatment courses. Other safety assessments including vital signs, physical examinations and laboratory assessments, as well as reported TEAEs and SAEs, both on- and off-treatment, showed that the intermittent repeated administration schedule was well tolerated, and the safety profile was comparable between the PGL4001 5 mg and 10 mg dosing groups. The number of TEAEs reported during treatment courses 2, 3 and 4 was lower than during treatment course 1, with no increase in frequency of any TEAE. The most frequently reported on-treatment TEAE was headache, and the most frequently reported on-treatment TEAE considered study medication-related was hot flush (mostly mild, none severe). The occurrence of hot flushes was in line with previous studies.

The table of adverse drug reactions during treatment course 1 has been updated to reflect the revised frequencies of several adverse drug reactions based on the pooled data from the four phase III studies (see SmPC section 4.8). When comparing repeated treatment courses, overall adverse reactions rate was less frequent in subsequent treatment courses than during the first one and each adverse reaction was less frequent or remained in the same frequency category (except for dyspepsia which was classified as uncommon in treatment course 3 based on one patient occurrence).

Overall, 34 SAEs occurred in 28 subjects, including 6 SAE reports of menorrhagia (5 were considered PGL4001- related). It is agreed that the occurrence of SAEs of menorrhagia could be expected as the population in the study are women with fibroid-related heavy menstrual bleeding. Similar frequencies were reported in studies PGL07-021 and PGL07-022 in the screening phase and in control groups. Three SAEs of myoma expulsion were reported (PT: uterine leiomyoma), which are part of the possible evolution of the fibroid disease and may reflect a reduction in the size of the myoma.

The analysis of TEAEs and provided SAEs did not raise any particular concerns regarding breast disorders during repeated intermittent treatment. The MAH has discussed the potential impact of ulipristal on the risk of breast cancer both with respect to selective progesterone receptor modulation as well as a result of a possible increase of estrogen levels. The current knowledge about Selective Progesterone Receptor Modulators (SPRM) does not indicate an increased risk for breast cancer.

The discontinuations in study PGL11-006 give no cause for concern. Overall, across the phase 3 studies with ulipristal acetate (PGL07-021–Part A, PGL07-022 – Part A, PGL09-026, PGL09-027 and PGL11-006 Part I; 1053 patients), TEAEs leading to study drug discontinuation occurred at a rate of 2.0% (1.9% for the 5 mg dose and 2.1% for the 10 mg dose).

2.6.2. Conclusions on clinical safety

Based on the available data related to endometrial safety after up to 4 treatment courses, no increased occurrence of more serious conditions of the endometrium such as hyperplasia with atypia or endometrial carcinoma was observed. The final study report from study PGL11-006 did not reveal any unexpected safety findings. It is reassuring that median endometrium thickness (7-8 mm) was similar to screening levels at all-time points during study and during the post-treatment follow-up. Furthermore, non-clinical carcinogenicity studies have become available after initial approval (see variation EMEA/H/C/2041/II/14). No neoplastic changes or other findings that would raise concern for long-term safety were observed in these studies. Thus, overall the safety profile is reassuring.

Additional safety data will be collected in the post-authorisation safety study (PGL14-001) following 1500 patients who intend a long-term treatment with UPA for up to 5 years as well as in the two already ongoing studies (PGL10-014 [already in the RMP], and PGL11-024). The currently ongoing study PGL11-024 (the second extension of PGL09-026, i.e. following PGL09-027) will provide safety and efficacy data of up to 8 treatment courses, i.e. data on 4 additional treatment courses further to the data submitted in this variation (see RMP).

2.6.3. PSUR cycle

The PSUR cycle remains unchanged.

The annex II related to the PSUR, refers to the EURD list which remains unchanged.

2.7. Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 13.2 could be acceptable if the applicant implements the changes to the RMP as described in the PRAC endorsed PRAC Rapporteur assessment report.

The CHMP endorsed this advice without changes.

The MAH implemented the changes requested in the RMP by PRAC and CHMP. The CHMP endorsed the changes to the Risk Management Plan version 13.3 with the following content (new text marked as underlined, deletions marked as strikethrough):

Safety concerns

Summary of safety concerns

Summary of safety concerns	
Important identified risks	Inappropriate management of endometrium thickening (unnecessary interventions or treatments) Inappropriate diagnosis of endometrial hyperplasia (mistaking PAEC for hyperplasia)
Important potential risks	Acute uterine bleeding requiring immediate intervention Drug Induced Liver Injury Treatment course beyond three months
Missing information	~~Treatment beyond three months~~ Long-term effects of prolonged treatment of the endometrium (including possible malignant changes) Delayed diagnosis of atypical endometrial hyperplasia or adenocarcinoma Impact on surgery Use in patients with moderate to severe hepatic impairment Use in patients with severe renal impairment

Pharmacovigilance plan

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
Prospective non interventional study (PASS) PGL10-014: A prospective multicenter non-interventional study of women treated with Esmya (ulipristal acetate) as pre-operative treatment of moderate to severe symptoms of uterine fibroids. (PREMYA, category 3)	Esmya use in "real world" practice	- Inappropriate management of endometrium thickening (unnecessary interventions or treatments) - Inappropriate diagnosis of endometrial hyperplasia (mistaking PAEC for hyperplasia) - Acute uterine bleeding requiring immediate intervention - Drug Induced Liver Injury (DILI) - Treatment course beyond three months - Delayed diagnosis of atypical	Started in Q1 2012	First yearly report submitted in May 2013 Second yearly report submitted in May 2014 Final study report planned Q1 2016 (4 years post-approval)

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
		endometrial hyperplasia or adenocarcinoma - Impact on surgery		
Retrospective non interventional study (PASS) PGL11-020: Esmya prescription patterns in Europe: A retrospective drug utilisation chart review study. (PRECISE, category 3)	Esmya use in "real world" practice	-Inappropriate management of endometrium thickening (unnecessary interventions or treatments) - Inappropriate diagnosis of endometrial hyperplasia (mistaking PAEC for hyperplasia) -Treatment course beyond three months - Impact on surgery	Started (EC submissions).	Interim study report submitted in Feb 2015 ~~planned Q1 2015~~ Final study report planned Q4 2015
Survey on effectiveness of educational programme for potential prescribers. (PREPAR; category 3)	Educational programme as risk minimisation measure	-Inappropriate management of endometrium thickening (unnecessary interventions or treatments) -Treatment course beyond three months - Delayed diagnosis of atypical endometrial hyperplasia or adenocarcinoma. -Inappropriate diagnosis of endometrial hyperplasia (mistaking PAEC for hyperplasia)	Started	survey report submitted March 2015 ~~Final survey report planned Q1 2015~~
Prospective, non-interventional study (PASS) PGL14-001: A prospective, non-interventional study to evaluate the long term safety of Esmya, in particular the endometrial safety, and the current	Esmya use in "real world" practice	-Inappropriate management of endometrium thickening (unnecessary interventions or treatments) - Inappropriate diagnosis of endometrial hyperplasia (mistaking PAEC for hyperplasia) - Acute uterine bleeding requiring immediate	Planned in Q4 2015	Yearly reports in Q1 2017, 2018, 2019, 2020, 2021 and 2022 Final report planned in Q1 2023 (8 years after variation approval)

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
prescription and management patterns of Esmya in a long term treatment setting. (PREMIUM, category 3)		intervention - Treatment course beyond three months - Long-term effects of prolonged treatment on the endometrium - Delayed diagnosis of atypical endometrial hyperplasia or adenocarcinoma - Impact on surgery		
Clinical trial PGL11-024: A Phase III, extension study of repeated intermittent 3-month courses of open-label of 10 mg ulipristal acetate. (PEARL extension 2, category 3)	Safety and efficacy in total eight 3-month treatment courses	- Long-term effects of prolonged treatment on the endometrium	Started	Final report in Q3 2015

Risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Inappropriate management of endometrium thickening (unnecessary interventions treatments)	*Warning in section 4.4 of SmPC:* *Pharmacodynamic properties in section 5.1 of SmPC* *Description of selected adverse reactions in section 4.8. of SmPC*	Educational material to prescribers (gynaecologists).
Inappropriate diagnosis of endometrial hyperplasia (mistaking PAEC for hyperplasia)	*Warning in section 4.4. of SmPC* *Description of selected adverse reactions in section 4.8. of SmPC* *Pharmacodynamic properties in section 5.1. of SmPC*	Educational material to prescribers and pathologists.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Acute uterine bleeding requiring immediate intervention	*Section 4.4.* *Section 4.8.*, Selected adverse reactions	None proposed.
Drug induced liver injury	This risk has not been confirmed in human.	None proposed.
Treatment course beyond three months	*Posology (section 4.2. of SmPC)* *Special warnings and precautions for use (section 4.4 of SmPC)* *Pharmacodynamic properties (section 5.1. of SmPC)*	Educational material to prescribers.
Long-term effects of prolonged treatment of the endometrium (including possible malignant changes)	~~*Indication restricted to pre-operative use (section 4.1 of SmPC)*~~ *Posology (section 4.2. of SmPC)* *Special Warnings and precautions for use (section 4.4 in the SmPC)* ~~*Pharmacodynamic properties (section 5.1 of SmPC)*~~	None proposed.
Delayed diagnosis of atypical endometrial hyperplasia or adenocarcinoma	*Special warnings and precautions for use in section 4.4. of SmPC* *Pharmacodynamic properties in section 5.1. of SmPC*	Educational material to prescribers and pathologists.
Impact on surgery	Impact of Esmya may be beneficial and/or adverse effect on the subsequent fibroid surgery. Since it is an unproven and rather an unlikely hypothetical risk, routine risk minimisation activities are considered not necessary at this stage.	None proposed.
Use in patients with moderate to severe hepatic impairment	*Posology and method of administration (section 4.2 in SmPC).* *Special warnings and precautions for use (section 4.4 in SmPC)* *Pharmacokinetic properties (section 5.2 in SmPC)*	None proposed.
Use in patients with severe renal impairment	*Posology and method of administration section 4.2 in SmPC)* *Special warnings and precautions for use (section 4.4 in SmPC)* ~~*Pharmacokinetic properties (section 5.2 in SmPC)*~~	None proposed.

2.8. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2 and 5.1 of the SmPC have been updated. Some changes were also made in section 4.4, e.g. the warning with regard to endometrial changes. In addition, section 4.8 of the SmPC has been updated with information from the new studies. The Package Leaflet has been updated accordingly.

3. Benefit-Risk Balance

Benefits

Beneficial effects

In short-term studies, i.e. one treatment course of 3 months, ulipristal acetate has shown a statistically significant difference in reduction in menstrual blood loss versus placebo and approximately 75% of the women were in amenorrhea after one treatment course with ulipristal acetate 5 mg/day. Patients treated with ulipristal acetate had a greater reduction in myoma size versus placebo. In comparison with the GnRH agonist leuprorelin, the effects of ulipristal acetate were overall of a similar magnitude.

The clinical data after more than two treatment courses in study PGL11-006 has now been provided along with data from study PGL09-027 (previously assessed data).

In study PGL11-006, 61.9% of patients on the 5 mg dose were in amenorrhea at the end of both treatment course 1 and 2; 48.7 % were in amenorrhea at the end of all four treatment courses. At the end of treatment course 4, 158 (69.6%) patients were assessed as being in amenorrhea. The proportion of subjects in amenorrhoea at the end of treatment course 4 was to some extent lower compared to at the end of course 2. However, the proportions are still considered to be of clinical relevance. In addition, 73.3 % of the patients on the 5 mg dose had controlled bleeding (no episodes of heavy bleeding and a maximum of 8 days of bleeding over 56 days) after treatment course 4.

The mean (median) PBAC scores associated with return of menstruation decreased after each subsequent treatment course. Both fibroid volume and uterine volume decreased during the study. The total volume of the 3 largest fibroids identified at screening was shown to decrease following the first treatment course, and to further decrease after each treatment course. The mean (median) percent change from baseline (screening 3) to visit 10 was -38% (-72%). By the end of treatment course 4, 81% had a $\geqslant$25% myoma volume reduction.

An improvement in quality of life measurements evaluated using the specific UFS-QoL symptom severity and HRQL scales was also showed. During the off-treatment interval, with resumption of menstruation the quality of life was slightly reduced compared to the end of each treatment course, but was still improved in comparison to baseline.

Uncertainty in the knowledge about the beneficial effects

Long term treatment has been studied up to 4 intermittent treatment courses (see SmPC section 4.2). Additional efficacy data will be available from the ongoing study PGL11-024 (the second extension of PGL09-026, i.e. following PGL09-027) will provide safety and efficacy data of up to 8 treatment courses, i.e. data on 4 additional treatment courses further to the available data (see RMP).

Risks

Unfavourable effects

Repeated doses of ulipristal acetate is reported in 1238 subjects of whom 1053 were exposed for ≥3 months to the target dose of 5 mg/day or higher, and 541 subjects were exposed for ≥ two 3-month treatment courses to the target does of 5 mg/day or higher. Totally 457 subjects were exposed to four 3-month treatment courses in completed study with 5 or 10 mg/day (when taking account of off-treatment intervals, equates to 21 months of treatment and monitoring).

Endometrial safety data are obtained from ultrasound examinations (endometrial thickness) and by biopsies (hyperplasia/carcinoma and non-physiological changes). The final study results of PGL11-006 were included with treatment courses 1 to 4 up to the end of the study follow-up visit, and with available data on women with endometrial thickness ≥ 16 mm. In long-term Phase III studies (PGL09-026/027 and PGL11-006), the total number of biopsies is 380, 3 months after discontinuation of 4 treatment courses. Excluding UPA+NETA subjects, the total number of adequate biopsies is 318, 3 months after discontinuation of 4 treatment courses.

In study PGL11-006, there were fewer subjects with endometrium thickness >16 mm after successive treatment courses. The frequency decreased from 7.4% to 1.5% from treatment course 1 to treatment course 4. The median endometrium thickness was similar to screening levels at all time-points during the study and post-treatment follow-up.

The frequency of non-physiological changes did not increase with repetition of treatment courses (observed in 17.8% and 13.3% of biopsies respectively following treatment courses 2 and 4). The data from this study confirmed a rapid reversibility of SPRM-associated non-physiological endometrial changes following completion of treatment and subsequent menstruation.

With respect to the biopsy results in the clinical studies, the frequency of hyperplasia in all phase 3 studies is low (0.89%) and, importantly, lower than the incidence in study population prior to treatment (1.82%). When looking at the incidence after 4 courses in study 006, the incidence was 0.59% with 5 out of 6 cases being reversible. Preliminary results from the ongoing Pearl extension 2 (8 treatment courses) have not shown any cases of hyperplasia, albeit in a small sample size. In addition, from a mechanistic point of view, it can be agreed that the risk of endometrial hyperplasia and cancer may be lower compared to a continuous oestrogen effect. Therefore, the risk of endometrial hyperplasia associated with the use of ulipristal acetate is considered as low and does not preclude an approval of repeated, intermittent treatment courses.

Uncertainty in the knowledge about the unfavourable effects

Long term safety has been studied up to 4 intermittent treatment courses (see SmPC section 4.2). Long-term safety data with particular attention to endometrial safety will be followed in three studies (PGL10-014, PGL11-024 and PGL14-001, see RMP).

Benefit-Risk Balance

Importance of favourable and unfavourable effects

Studies evaluating treatment up to 4 intermittent treatment courses studies have shown that ulipristal acetate treatment results in amenorrhoea in a substantial part of the women. Available data have shown that the effects are maintained over up to four treatment courses where approximately 73 % of women experienced controlled bleeding. Reductions in myoma and uterine volume are observed and clinically relevant effects on pain and quality of life outcomes are also shown. Thus, it is considered sufficiently demonstrated that the effect of Esmya is maintained during repeated intermittent use which is assessed as important.

The adverse event profile is rather benign and data up to 4 intermittent treatment cycles have not shown any new or unexpected adverse events.

The incidence and prevalence of hyperplasia with ulipristal acetate are below 1% and compares with published literature regarding prevalence. Repeated treatment with ulipristal acetate courses did not increase the occurrence of more serious conditions of the endometrium such as hyperplasia with atypia or endometrial carcinoma. The action of ulipristal acetate on the endometrium is specific and different from an unopposed oestrogen effect. Ulipristal acetate is not carcinogenic in experimental animals at sufficiently large exposure margins compared to human exposure. The risk of endometrial hyperplasia associated with the use of ulipristal acetate is considered as low and does not preclude an approval of repeated, intermittent treatment courses.

Benefit-risk balance

The Benefit/Risk for the proposed extension of indication for Esmya for intermittent treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age is considered positive.

Discussion on the benefit-risk balance

Esmya is currently approved for the pre-operative treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age with a treatment duration limited to a maximum of two treatment courses of 3 months each. The limitation in duration of treatment was due to lack of long term safety data. Surgery may not be a suitable option for all patients, e.g. for medical or personal reasons or if the woman is peri-menopausal and would rather wait that the symptoms of uterine fibroids decrease as result of menopause. Thus, a continued medical treatment of fibroids would be valuable and currently no medical treatment is approved in this indication.

Safety and efficacy data on the use of Esmya for intermittent treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age is available for up to 4 intermittent treatment courses. Further long-term safety and efficacy data will be available from several studies as reflected in the risk management plan.

Women who get symptomatic relief (less bloating & discomfort due to reduced fibroid size and better energy due to less heavy bleeding) might be inclined to use Esmya persistently without a break. This type of use poses a risk since intermittent use allows/induces a type of withdrawal bleed, which should offset any developing endometrial hyperplasia. In order to minimise the risk of occurrence of persistent use beyond 3 months, stringent risk minimisation activities were initiated at the time of initial MA and are still undertaken. The treatment should not be longer than 3 months continuously as the risk on endometrium is unknown if continued longer and that it must be intermittent in case of the proposed repeated intermittent use (see SmPC sections 4.2, 4.4). Educational material is in place to increase awareness that each Esmya treatment course should be limited to 3 months. From the presented post marketing data the risk seems limited with a low number of cases and no detrimental reported adverse events.

The discrepancy in diagnosing endometrial hyperplasia is a well-described fact and not specific to the follow-up of treatment with ulipristal acetate. The educational material to prescribers and pathologists has been updated to reflect the extended indication. The educational program in combination with the additional pharmacovigilance activities in the RMP are considered sufficient and will provide appropriate measures on reducing the risk of inappropriate management of endometrium thickening and inappropriate diagnosis of endometrial hyperplasia as well as long term treatment with ulipristal acetate.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation(s) to the terms of the Marketing Authorisation, concerning the following change:

Variation requested		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II and IIIB

Extension of the indication to include intermittent treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age; consequently, the sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC have been updated. The Package Leaflet has been updated accordingly. Furthermore, the key elements of the educational material in Annex II have been revised.

The requested variation proposed amendments to the Summary of Product Characteristics, Annex II and Package Leaflet.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Extension of the indication to include intermittent treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age; consequently, the sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC have been updated. The Package Leaflet has been updated accordingly. Furthermore, the key elements of the educational material in Annex II have been revised.

Summary

This variation extends the use of Esmya to include intermittent treatment of moderate to severe symptoms of uterine fibroids based on data from two phase III studies. In that context, safety information has also been updated with recommendations for periodic monitoring of the endometrium and information on the management of altered bleeding (inter-menstrual bleeding) and hyperplasia (with and without atypia).

Please refer to Scientific Discussion 'Esmya-H-C-2041-II-28'