AusPAR Attachment 2

Extract from the Clinical Evaluation Report for ulipristal acetate

Proprietary Product Name: Esmya

Sponsor: Vifor Pharma Pty Ltd

Date of first round report: October 2015

Date of second round report: January 2016

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About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.

- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.

- For the most recent Product Information (PI), please refer to the TGA website <https://www.tga.gov.au/product-information-pi>.

Contents

List of abbreviations

Abbreviation	Meaning
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Transaminase
AST	Aspartate Transaminase
AUC_{0-t}	Area under the plasma concentration versus time curve from time zero to the time (t) corresponding to the last quantifiable concentration
$AUC_{0-\infty}$	Area under the concentration-time curve from time zero up to infinity with extrapolation of the terminal phase
BMI	Body mass index
CFS	Change from screening
C_{max}	Maximum plasma concentration
CMI	Consumer Medicine Information
CHMP	Committee for the Medicinal Products for Human Use
E2	Oestradiol
ECG	Electrocardiogram
EMA	European Medicines Agency
FAS	Full Analysis Set
FSH	Follicle Stimulating Hormone
GnRH	Gonadotrophin-Releasing Hormone
Hb	Haemoglobin
LLN	Lower Limit of Normal
MRI	Magnetic Resonance Imaging
NETA	Norethisterone acetate
PAEC	Progesterone receptor modulator Associated Endometrial Changes
PBAC	Pictorial Bleeding Assessment Chart

Abbreviation	Meaning
PD	Pharmacodynamic
PK	Pharmacokinetic
PI	Product Information
PP	Per Protocol
PSUR	Periodic Safety Update Report
PT	Preferred Term
RMP	Risk Management Plan
SD	Standard Deviation
SAE	Serious Adverse Event
SF-MPQ	Short-form McGill Pain questionnaire
SOC	System Organ Class
SPRM	Selective Progesterone Receptor Modulator
TEAE	Treatment Emergent Adverse Event
TSH	Thyroid Stimulating Hormone
TVUS	Trans-vaginal Ultrasound
UFS-QoL	Uterine Fibroid Symptom and Health-Related Quality of Life Questionnaire
ULN	Upper Limit of Normal
UPA/UA	Ulipristal acetate
US	Ultrasound
VAS	Visual Analogue Scale

1. Introduction

This is an application to extend the indications for ulipristal acetate.

1.1. Drug class and therapeutic indication

Ulipristal acetate is a selective progesterone receptor modulator, whose main pharmacodynamic action is to reversibly block the progesterone receptor in target tissues, including the uterus, ovaries and hypothalamus.

The approved indication for ulipristal acetate 30 mg tablet (EllaOne) is:

> *Emergency contraception within 120 hours (5 days) of unprotected sexual intercourse or contraceptive failure.*

The proposed indication for ulipristal acetate 5 mg tablet is:

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

1.2. Dosage forms and strengths

The following dosage forms and strengths are currently registered:

> *EllaOne ulipristal acetate 30 mg tablet blister pack*

The submission proposes registration of the following dosage forms and strengths:

> *Esmya ulipristal acetate 5 mg tablet*

1.3. Dosage and administration

The proposed dosage and administration for Esmya ulipristal acetate 5 mg tablet is:

> *The treatment consists of one tablet of 5 mg to be taken orally once daily for treatment courses of up to 3 months each. Long-term treatment has been studied up to 4 intermittent treatment courses.*

> *Treatment courses should be intermittent. The treating physician should instruct the patient of the need of treatment free intervals. Re-treatment should start at the earliest during the second menstruation following the previous treatment course completion.*

> *Treatment courses should always be started during the first week of menstruation.*

> *If a patient misses a dose, the patient should take ulipristal acetate as soon as possible. If the dose was missed by more than 12 hours, the patient should not take the missed dose and simply resume the usual dosing schedule.*

2. Clinical rationale

Uterine fibroids (myomas, leiomyomata) are benign, monoclonal tumours of the myometrium. Uterine fibroids are the most common gynaecological tumour in pre-menopausal women, reported to occur in up to 70% of Caucasian women by age 50 years[1] with a peak incidence at 40-50 years of age. Risk factors for the development of uterine fibroids include nulliparity, obesity, polycystic ovarian syndrome, hypertension, Afro-Caribbean descent and family history

of fibroids. Leiomyomata are under the influence of oestrogen and progesterone, and mostly regress after menopause.

Uterine fibroids vary in size and location (sub-mucosal, intramural, or sub-serosal) and can be single or multiple. Whilst the majority of fibroids are asymptomatic and followed without intervention, up to 50% of women with uterine fibroids have symptoms, most commonly heavy uterine bleeding. Other presentations can include bulk symptoms (pelvic pressure, urinary urgency and frequency), iron deficiency anaemia and subfertility.

Treatment options are based on symptoms, age, reproductive considerations, size and location of myomas. Surgical management is the mainstay of treatment for uterine fibroids. In Australia, uterine fibroids are one of the most common indications for hysterectomy,[1] the definitive procedure for fibroids. Uterus preserving surgical options include myomectomy, uterine artery embolisation and endometrial ablation.

Currently, there are no effective long-term non-surgical treatment options for of uterine fibroids. Whilst GnRH agonists are effective prior to fibroid surgery in reducing fibroid volume and aiding correction of anaemia, longer term use is limited due to menopausal symptoms and bone demineralisation resulting from the suppression of oestrogen to castration like levels. In Australia, the GnRH agonist goserelin 3.6 mg implant is approved for the management of uterine fibroids as an adjunct to surgery for a period of 3 to 6 months. The registered indication is:[2]

> *In the management of fibroids, ZOLADEX shrinks the lesions and reduces the symptoms, including pain. ZOLADEX also increases the haemoglobin concentration and haematocrit in women with anaemia attributable to menorrhagia. It is used as an adjunct to surgery to facilitate the operative technique and reduce operative blood loss.*

Hormonal therapies, such as combined hormonal contraceptives and progestational agents, are used for symptomatic management of heavy uterine bleeding, but are not considered effective in the treatment of uterine fibroids. The levonorgestrel-releasing IUD (Mirena) is widely used for the control of heavy menstrual bleeding, however, is contraindicated if the uterine cavity is distorted by fibroids[3] and there are suggestions in the literature that expulsion rates may be higher in the presence of submucosal fibroids.[4]

Ulipristal acetate is a selective progesterone receptor modulator (SPRM). The Sponsor states by acting as a progesterone receptor antagonist, ulipristal deprives the uterine fibroids of growth stimulation due to progesterone, and can induce amenorrhoea by interacting with progesterone receptors on the endometrium. Further, the Sponsor states ulipristal acetate will provide an alternative treatment option to surgery, or short-term GnRH agonist use, for the management of uterine fibroid symptoms over a longer period of time. The clinical rationale is considered acceptable.

3. Contents of the clinical dossier

3.1. Scope of the clinical dossier

The submission contained the following clinical information:

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[1] Varol N, Healey M, Tang P, Sheehan P, Maher P, Hill D. Ten-year review of hysterectomy morbidity and mortality: can we change direction? Aust NZ J Obstet Gynaecol. 2001; 41:295-302.
[2] Australian PI Zoladex 3.6 mg Implant.
[3] Australian PI Mirena.
[4] Ikomi A, Pepra EF. Efficacy of the levonorgestrel intrauterine system in treating menorrhagia: actualities and ambiguities. J Fam Plann Reprod Health Care. 2002 Apr;28(2):99-100.

- 24 clinical pharmacology studies, including 17 that provided pharmacokinetic data and 7 that provided pharmacodynamic data.
- 5 efficacy and safety studies – PGL11-006, PGL09-026 and extension PGL09-027 and PGL11-024, PGL07-021, PGL07-022.
- 2 Phase II studies – PGL-N-0090 and PGL-N-0287.
- 5 PSURs, literature references.

3.2. Paediatric data

The submission did not include paediatric data. The sponsor states the EMA granted a PIP waiver for girls from age menarche to less than 18 years.

3.3. Good clinical practice

The Sponsor states all trials were performed in accordance with the principles of Good Clinical Practice.

4. Pharmacokinetics

4.1. Studies providing pharmacokinetic data

Table 1 shows the studies relating to each pharmacokinetic topic. The majority of these studies have been submitted previously to the TGA. Study summaries are provided for those studies evaluated in this submission.

Table 1. Submitted pharmacokinetic studies.

PK topic	Subtopic	Study ID
PK in healthy adults	General PK - Single dose	PGL-H-512 (HRA2914-512)[a] PGL-H-501 (HRA2914-501)[a] PGL-H-503 (HRA2914-503, Passaro et al., 2003)[a] PGL-H-504 (HRA2914-504)[a] PGL09-015 (HRA2914-553)[a]
	- Multi-dose	PGL09-023 (HRA2914-545)[a]
	Bioequivalence† - Single dose	PGL-H-516 (HRA2914-516)[a] PGL09-004
	- Multi-dose	PGL-H-650 (HRA111014-001)[a]
	Food effect	PGL-H-512 (HRA2914-008)[a]
PK in special populations	Target population § - Single dose	Nil

PK topic	Subtopic	Study ID
	Hepatic impairment	PGL-W-001
	Renal impairment	Nil
	Elderly	Nil
Genetic/gender related PK	Lactating females	PGL-H-514 (HRA2914-514)[a]
PK interactions	Erythromycin	PGL-09-022 (HRA2914-549)[a]
	Esomeprazole	PGL11-002 (HRA2914-546)[a]
	Fexofenadine	PGL-W-002 (HRA2914-548)[a]
	Ketoconazole	PGL-W-003 (HRA2914-547)[a]
	Rifampicin	PFL-H-551 (HRA2914-551)[a]

† Bioequivalence of different formulations.

§ Subjects who would be eligible to receive the drug if approved for the proposed indication.

a Evaluated in the UPA (EllaOne) submission.[5]

The TGA Clinical Evaluator for the original marketing authorisation application stated none of the pharmacokinetic studies had deficiencies that excluded their results from consideration.

4.2. Summary of pharmacokinetics

The information in the following summary is derived from conventional pharmacokinetic studies unless otherwise stated.

The pharmacokinetic profile of ulipristal acetate (UPA) has been described in the original marketing authorisation application for ulipristal acetate 30 mg (EllaOne), with the majority of studies submitted in the current dossier evaluated in this submission. The additional PK studies submitted in support of the ulipristal acetate 5 mg application will be discussed below.

4.2.1. Pharmacokinetics in healthy subjects

4.2.1.1. Absorption

Study PGL09-004 was an open, randomised, 2-period crossover study comparing the bioavailability of a single oral dose of UPA wet granulation (WG) tablets and ulipristal (DC) direct compression tablets at two different dose strengths (5 mg and 10 mg) in 64 healthy female volunteers.

The main PK parameters for the UPA 5 mg and 10 mg DC formulation (and metabolite PGL4002) are summarised in Tables 2 and 3 below.

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[5] Passaro MD, et al. Luteal phase dose-response relationships of the antiprogestin CDB-2914 in normally cycling women. *Hum Reprod.* 18: 1820-1827 (2003).

Table 2. Summary statistics for PK parameters for single dose ulipristal acetate 5 mg and 10 mg (DC and WG formulations).

Treatment	Mean (SD) $AUC_{0-\infty}$ (h*ng/mL)	Mean (SD) AUC_{0-t} (h*ng/mL)	Mean C_{max} (ng/mL)
UPA 5 mg (DC formulation)	68.5 (33.0)	61.3 (31.7)	23.5 (14.2)
UPA 5 mg (WG formulation)	69.4 (34.3)	62.2 (33.7)	25.0 (15.0)
UPA 10 mg (DC formulation)	141.4 (88.1)	134.0 (83.8)	50.0 (34.4)
UPA 10 mg (WG formulation)	140.5 (82.1)	131.8 (78.7)	51.0 (35.1)

Table 3. Summary statistics for PK parameters for PGL4002 following single dose ulipristal acetate 5 mg and 10 mg (DC and WG formulations).

Treatment	Mean (SD) $AUC_{0-\infty}$ (h*ng/mL)	Mean (SD) AUC_{0-t} (h*ng/mL)	Mean C_{max} (ng/mL)
PGL4002 (UPA 5 mg DC formulation)	29.4 (12.9)	26.0 (12.0)	9.0 (4.4)
PGL4002 (UPA 5 mg DC formulation)	29.3 (12.3)	26.1 (11.5)	9.9 (6.0)
PGL4002 (UPA 10 mg DC formulation)	68.2 (31.5)	63.6 (30.1)	20.6 (10.8)
PGL4002 (UPA 10 mg DC formulation)	68.1 (28.3)	63.3 (26.9)	21.7 (11.3)

Bioequivalence was demonstrated for the DC and WG formulations for both doses with respect to AUC0-∞ and AUC0-t. For Cmax , the upper limit of the 90% CI for was just outside the accepted upper limit of bioequivalence for both dose strengths (1.26 for the 5 mg group and 1.27 for the 10 mg group). The Sponsor states this was due to wide intra-subject variability. The EMA Evaluator considered the deviation to be small and not likely to be of relevance, and this Evaluator concurs with these comments. The Phase III studies were conducted with the final to-be-marketed formulation.

4.2.1.2. Bioavailability

Influence of food

The Clinical Evaluator for this submission noted food decreased the absorption of ulipristal, but increased the overall bioavailability. There are no studies with ulipristal 5 mg tablets, however the Sponsor states "the effect is expected to be similar" and not of clinical relevance with daily

administration of UPA 5 mg. There are no specific recommendations regarding food in the EllaOne PI,[6] EU SmPC for Esmya,[7] or in the proposed PI.

Dose proportionality

In Study PGL09-023, the Clinical Evaluator noted the PKs for UPA were not dose proportional in the dose range 10-50 mg, although the EMA Evaluator states the deviation from dose proportionality was not very large.

However, dose proportionality for the 5 mg and 10 mg UPA doses was demonstrated in Study PGL09-004.

Bioavailability during multiple-dosing

The Clinical Evaluator states there was no evidence of unpredictable accumulation with multiple dosing in the range 10-50 mg over 10 days. Further, there was no evidence of changes in metabolism of UPA or the main metabolite PGL4002 over this 10 day period.

4.2.1.3. Metabolism

The Clinical Evaluator notes UPA is predominantly metabolised by CYP3A4, there are no active metabolites reported, and UPA clearance is predominantly non-renal.

4.2.2. Pharmacokinetics in the target population

There were no PK studies in the target population. However, the EMA Evaluator stated as Esmya is proposed for use in fertile women, the population included in the PK studies, ie. healthy females aged 18-50, was considered adequate. This Evaluator agrees with this conclusion.

4.2.3. Pharmacokinetics in other special populations

4.2.3.1. Pharmacokinetics in subjects with impaired hepatic function

There were no studies in subjects with hepatic impairment submitted as part of the original marketing authorisation application for UPA 5 mg in the EU. However given CYP-mediated metabolism, hepatic impairment is considered likely to alter the PKs of UPA and thus a study to assess PKs in volunteers with hepatic impairment was to be conducted as part of the RMP. The Sponsor has submitted Study PGL-W-001, an open-label prospective study to compare the PKs of a single oral dose of 10 mg UPA in 8 female subjects with moderately impaired hepatic function with 8 healthy subjects with normal hepatic function.

Total (bound and unbound) UPA $AUC_{0-\infty}$ was 37% lower, and Cmax 57% lower in subjects with moderate hepatic impairment than those with normal hepatic function. A similar trend was observed for the main metabolite PGL4002 ($AUC_{0-\infty}$ 39% lower and Cmax 51% lower in hepatic impaired subjects). The Sponsor noted the PK results from this study were variable, with large overlap in PK parameters between the hepatic impaired and control groups. The Sponsor states further the study was inconclusive as subjects did not have adequate deviations in markers from impaired hepatic function (albumin, bilirubin, prothrombin time).

4.2.3.2. Pharmacokinetics in subjects with impaired renal function

There were no data.

4.2.3.3. Pharmacokinetics according to age

There were no data.

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[6] Australia PI EllaOne (Version 06 – March 2015).

[7] EU SmPC Esmya.

4.3. Evaluator's overall conclusions on pharmacokinetics

The majority of studies regarding the PKs of UPA have been previously evaluated by the TGA in the original marketing authorisation. The Clinical Evaluator for this submission concluded the PKs for UPA to have been adequately described for the target population (women of child bearing potential) and this argument is endorsed by the EMA Evaluator for UPA 5 mg.

Study PGL-W-001 was not considered conclusive regarding use in moderate hepatic impairment due to markers for same deemed inadequate. The PI recommends no dosage adjustment in mild hepatic impairment, with use in moderate and severe hepatic impairment not recommended unless the patient is closely monitored. The EMA Evaluator considers this recommendation justified although did not consider a strict contraindication necessary as UPA "is not a substance with a narrow therapeutic window and 10-fold higher doses (50 mg/day) have been administered without serious safety concerns." This Evaluator agrees with this comment.

There were no studies in patients with renal impairment. As such, UPA 5 mg is not recommended in patients with severe renal impairment unless closely monitored.

5. Pharmacodynamics

5.1. Studies providing pharmacodynamic data

Table 4 shows the studies relating to each pharmacodynamic topic.

Table 4. Submitted pharmacodynamic studies.

PD Topic	Subtopic: Study ID
Primary Pharmacology	Effect on luteolysis: PGL-H-503 (HRA2914-503), Passaro *et al.,* 2003[a]
	Effect on folliculogenesis: PGL-H-505 (HRA2914-505)[a]
	Effect on menstrual cycle: PGL-H-506 (HRA2914-506)[a]
	Effect on ovulation:
	PGL-H-554 (HRA2914-554)[a]
	PGL-H-510 (HRA2914-510)[a]
	PGL-P-349
	Effect on follicle rupture: PGL-H-511 (HRA2914-511)[a]

[a] Evaluated in the UPA (EllaOne) submission.[8]

The TGA Clinical Evaluator of the original marketing authorisation submission stated none of the pharmacodynamic studies had deficiencies that excluded their results from consideration.

5.2. Summary of pharmacodynamics

5.2.1. Pharmacodynamic effects

The studies listed above have been evaluated in the original marketing authorisation.

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[8] Passaro MD, et al. Luteal phase dose-response relationships of the antiprogestin CDB-2914 in normally cycling women. *Hum Reprod.* 18: 1820-1827 (2003).

Additional PD data were provided in the Phase III studies PGL07-021 and PGL07-022. Trough concentrations of ulipristal and metabolite PGL4002 were obtained at weeks 5, 9 and 13 of these studies. The EMA Evaluator concluded there was no correlation observed between mean trough levels of UPA and/or PGL4002 and endometrial thickness, total myoma volume or uterine volume. This Evaluator agrees with this conclusion.

The Sponsor submitted the published study by Brache and colleagues (listed as Study PGL-H-649). These authors report a prospective, controlled, open-label, multi-centre study to examine the effectiveness and safety of a contraceptive vaginal ring containing ulipristal in 39 healthy women aged 21–40 years old. Study participants underwent a 12-week treatment period of continuous use of the ulipristal containing vaginal ring (delivering 600-800 mcg/day). These authors reported ovulation was documented in 32% subjects, and observed a correlation between serum ulipristal levels and inhibition of ovulation. Brache and colleagues state there was no evidence of endometrial hyperplasia, although progesterone receptor modulator associated endometrial changes (PAEC) were frequently observed (41%).

5.3. Evaluator's overall conclusions on pharmacodynamics

The Clinical Evaluator for this submission stated the PD studies examined the ulipristal dose range 10-200 mg as a single dose, and concluded there were dose dependent effects in follicular growth, follicular rupture, endometrial growth and cycle length, although states these effects were not significant at the 10 mg dose level.

6. Dosage selection for the pivotal studies

Regarding dose selection for pivotal study PGL11-006, the sponsor states both the 5 mg and 10 mg doses of UPA demonstrated efficacy over a single 3 month treatment course; it was hypothesised the 10 mg dose may be advantageous in repeated intermittent administration.

A dose of UPA 10 mg daily was used in Study PGL09-027 (commenced prior to Study PGL11-006). The sponsor states the results of the short term studies PGL07-021 and PGL07-022, using both 5 mg and 10 mg UPA doses, were not known at the time of study design of PGL09-026 and PGL09-027, and the 10 mg dose was chosen as:

> as it was hypothesised that a 10 mg dose might have advantages in terms of efficacy for a repeated intermittent treatment.

7. Clinical efficacy

There are five Phase III studies provided in the dossier. The two studies PGL11-006 and PGL09-027 (extension of PGL09-026) are considered pivotal as these two studies provide data for long-term administration of UPA for uterine fibroids. Studies PGL07-021, PGL07-022, and PGL09-026 provide data for short term (3 month) pre operative use of UPA and are considered supportive. A summary of the key study design parameters for the Phase III studies is shown below in Table 5.

Table 5. Summary of Phase III studies key design parameters

Phase III Study	Design	Duration	N	Dose of UPA	Age range	Key demographics / disease characteristics	Key inclusion criteria

Phase III Study	Design	Duration	N	Dose of UPA	Age range	Key demographics / disease characteristics	Key inclusion criteria
PGL11-006	Double-blind, parallel-group	4 x 84 days	451	5 mg (n=228) or 10 mg (n=223) daily	18-50 inclusive	94.2% white; mean age 41.5 years; mean BMI 25.2; 94.7% of child-bearing potential; mean (median) PBAC score > 100 at screening	PBAC score > 100, myomatous uterus < 16 weeks, largest fibroid 3-12 cm diameter inclusive
PGL09-026	Open-label for UPA	90 days	209	10 mg daily	18-48 inclusive	85.1% white; mean age 40.0 years; mean BMI 25.4; 96.0% of child-bearing potential; mean (median) PBAC score at baseline = 319 (216).	myomatous uterus < 16 weeks, at least one myoma ≥ 3 cm diameter, nil larger than 10 cm, eligible for hysterectomy or myomectomy
PGL09-027 (extension of PGL09-026)		Further 3 x 90 day courses	132				
PGL07-021	Double-blind, placebo controlled	13 weeks	194	5 mg (n=96) or 10 mg (n=98) daily	18-50 inclusive	88.0% white; mean age 41.6 years; mean BMI 25.3; 92.1% of child-bearing potential; mean (median) PBAC score at baseline = 452 (361).	PBAC score > 100, myomatous uterus ≤ 16 weeks gestation equivalent, at least one myoma ≥ 3 cm diameter, nil larger than 10 cm, fibroid related

Phase III Study	Design	Duration	N	Dose of UPA	Age range	Key demographics / disease characteristics	Key inclusion criteria
							anaemia defined as Hb ≤ 10.2g/dL, eligible for surgery
PGL07-022	Double blind, double dummy, active comparator controlled (leuprorelin)	13 weeks	307	5mg (n=102) or 10 mg (n=103) daily	18-50 inclusive	Mean age 40.4 years; mean BMI 25.5; 96.3% of child-bearing potential; mean (median) PBAC score at baseline = 370 (282)	PBAC score > 100, myomatous uterus ≤ 16 weeks gestation equivalent, at least one myoma ≥ 3 cm diameter, nil larger than 10 cm, eligible for surgery.

The pictorial bleeding assessment chart (PBAC) is a validated scoring method to objectively measure menstrual blood loss, and was used as a measure of uterine bleeding for the key efficacy endpoints in the Phase III studies. Heavy bleeding is defined as PBAC > 100 (equivalent to over 80 mL blood loss).

Fibroid and uterine volumes were assessed by trans vaginal ultrasound (TVUS) in all Phase III studies, except for Study PGL-021, where MRI was the imaging modality of choice. The sponsor states ultrasound is the routine investigation of choice in patients presenting with heavy uterine bleeding/fibroids, however MRI is more precise with regard to measurements of fibroids and was used in Study PGL07-021 as change in total fibroid volume was a co-primary endpoint. The sponsor states this was based on discussions with various EU regulators.

7.1. Pivotal efficacy studies

7.1.1. Study PGL11-006

The pivotal study PGL11-006 was a Phase III randomised, double-blind, multi-centre study to assess the efficacy and safety of repeated 12 week courses of daily UPA (5 mg or 10 mg) for long-term management of symptomatic uterine fibroids. The study population consisted of 451 pre-menopausal women with symptomatic uterine myoma(s) and heavy bleeding (8-day PBAC score > 100 at screening).

Study participants were randomised in 1:1 ratio to received UPA 5 mg daily (n=228) or 10 mg daily (n=223), for four courses (12 weeks, [84 days] per course). Each course was separated by

a drug free interval until the start of the second menstruation from the end of the previous treatment course. The rationale for the intermittent treatment courses was stated by the Sponsor 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. The Sponsor states there was no placebo arm as this as considered unethical given the duration of the study, and no active comparator available for long-term use. These justifications are considered acceptable by this Evaluator.

Study medication was administered 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. Patients completed the PBAC after each of the 4 treatment courses (4 x 8 days). Bleeding occurring outside this time frame was recorded in the subject diary. Key inclusion/exclusion criteria are provided

The study was conducted in two parts. In Part I of the study, the primary efficacy endpoint was the percentage of subjects in amenorrhoea at the end of both treatment courses 1 and 2. The primary efficacy endpoint for Part II of the study was the percentage of subjects who were in amenorrhoea at the end of all four treatment courses. Amenorrhoea was defined as no more than 1 day of spotting within a 35-day interval. Sensitivity analyses were performed for both endpoints imputing missing amenorrhoea assessments as a failure (not in amenorrhoea) or as a success (in amenorrhoea)].

There were multiple secondary efficacy endpoints assessing the effect of UPA 5 mg and 10 mg doses on uterine bleeding pattern, myoma volume, pain and quality of life.

Statistical methods are discussed. It is noted there were no adjustments made for multiplicity. Although there were two primary endpoint analyses (end of Part I and end of Part II, the former a subset of the latter), the Sponsor states given the main planned use of the data from the study (ie. assessing the sustained efficacy and safety of intermittent repeated courses of UPA in the treatment of uterine myoma), no multiplicity adjustment for the efficacy comparisons was necessary. Secondary endpoints were analysed as supportive results.

The results of the primary efficacy endpoints were (FAS 1 population):

- Part I
  - 384 subjects had a non-missing amenorrhoea assessment at the end of treatment courses 1 and 2 (n=197 in the 5 mg group and n=187 in the 10 mg group). Of these subjects, 72.7% of subjects in the 10 mg group and 61.9% of subjects in the 5 mg group were in amenorrhoea (treatment difference 10 mg vs. 5 mg = 10.8% [95% CI: 1.5%, 20.1%, p=0.032]).
  - Sensitivity analyses yielded the following results:
    - for sensitivity analysis 1 (missing amenorrhoea assessments at the end of treatment courses 1 and/or 2 were imputed as failure [not in amenorrhoea]), 53.5% and 61.0% of subjects in the 10 mg and 5 mg groups respectively were in amenorrhoea at the end of treatment courses 1 and 2 (treatment difference 10 mg vs. 5 mg = 7.5% [95% CI: -1.6%, 16.6%; p=0.131]).
    - for sensitivity analysis 2 (missing amenorrhoea assessments at the end of treatment courses 1 and/or 2 were imputed as success [in amenorrhoea]), there were 75.3% of subjects in the 10 mg group and 63.6% of subjects in the 5 mg group who were in amenorrhoea at the end of treatment courses 1 and 2 (treatment difference 10 mg vs. 5 mg = 11.7% [95% CI: 3.3%, 20.2%; p=0.009]).
- Part II
  - 380 subjects had a non-missing amenorrhoea assessment at the end of all four treatment courses (n=195 and n=185 subjects in the 5 mg and 10 mg groups

respectively). There were 60.5% of subjects in the 10 mg group and 48.7% of subjects in the 5 mg group in amenorrhoea at the end of four treatment courses (treatment difference 10 mg vs. 5 mg = 11.8% [95% CI: 1.9%, 21.8%; p= 0.027]).

– Sensitivity analyses yielded the following results:

▪ for sensitivity analysis 1 (missing amenorrhoea assessments at the end of treatment courses 1, 2, 3 and/or 4 were imputed as failure [not in amenorrhoea]), 41.7% and 50.2% of subjects in the 5 mg and 10 mg groups respectively were in amenorrhoea at the end of all four treatment courses (treatment difference 10 mg vs. 5 mg = 8.6% [95% CI: -0.6%, 17.7%; p=0.084]).

▪ for sensitivity analysis 2 (missing amenorrhoea assessments at the end treatment courses 1, 2, 3 and/or 4 were imputed as success [in amenorrhoea]), 61.0% of subjects in the 10 mg group and 49.1% of subjects in the 5 mg group, respectively were in amenorrhoea at the end of all four treatment courses (treatment difference = 11.9% [95% CI: 2.7%, 21.0%; p=0.015]).

The results of the key secondary efficacy endpoints were:

• Uterine bleeding endpoints

– the percentage of patients in **amenorrhoea** at the end of each treatment course was reported for:

▪ 71.8% in the 5 mg group and 82.6% in the 10 mg group for treatment course 1.

▪ 74.1% in the 5 mg group and 82.2% in the 10 mg group for treatment course 2.

▪ 73.3% in the 5 mg group and 78.3% in the 10 mg group for treatment course 3.

▪ 69.6% in the 5 mg group and 74.5% in the 10 mg group for treatment course 4.

A statistically significant treatment difference (10 mg vs. 5 mg) was observed for treatment course 1 only (p=0.011) (Table 6).

Table 6. Study PGL11-006 - Analysis of Subjects in Amenorrhoea at the End of Each Treatment Course (Full Analysis Set 1).

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.

- **controlled bleeding** (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) was reported for:
  – 81.1% of subjects in the 5 mg group and 86.0% of subjects in the 10 mg group after treatment courses 1 and 2 (treatment difference 10 mg vs. 5 mg = 5.0% [95% CI: -2.7%, 12.6%; p= 0.263]).
  – 67.1% of subjects in the 5 mg group and 71.9% of subjects in the 10 mg group after all four treatment courses (treatment difference 10 mg vs. 5 mg = 4.8% [95% CI: -5.5%, 15.2%; p=0.430]).
  – controlled bleeding after each treatment course:
    - 88.3% in the 5 mg group and 93.4% in the 10 mg group for treatment course 1.
    - 87.9% in the 5 mg group and 88.0% in the 10 mg group for treatment course 2.
    - 81.2% in the 5 mg group and 80.1% in the 10 mg group for treatment course 3.
    - 73.3% in the 5 mg group and 75.0% in the 10 mg group for treatment course 4.

- The **median time to amenorrhoea** during treatment courses 1, 2, 3 and 4 was as follows (Table 6).
  – 5.0 days and 4.0 days for the 5 mg and 10 mg groups respectively for treatment course 1.
  – 5.0 days and 6.0 days for the 5 mg and 10 mg groups respectively for treatment course 2.
  – 6.0 days for both the 5 mg and 10 mg groups for treatment course 3.
  – 5.0 days for both the 5 mg and 10 mg groups for treatment course 4.

- Reductions in blood loss during the first menstrual bleed were observed after treatment courses 1, 2 and 4 for both groups (not reported post treatment course 3). The median change from baseline in PBAC scores were:
  – -87.0 for the 5 mg group and -85.0 for the 10 mg group post treatment course 1.
  – -95.0 for the 5 mg group and -109.5 for the 10 mg group post treatment course 1.
  – -118.0 for the 5 mg group and -121.0 for the 10 mg group post treatment course 1.

There was no statistically significant difference in median change from baseline in PBAC between the 5 mg and 10 mg groups.

- Fibroid endpoints

Reductions in myoma volume and uterine volume were observed in both the 5 mg and 10 mg groups at the end of treatment course 2 and treatment course 4 as follows:

Table 7. Summary of myoma volume parameters (FAS 1 set).

Time point	Fibroid volume parameter	Ulipristal 5 mg group (n=228)	Ulipristal 10 mg group (n=223)	Total (n=451)
End of treatment course 2[a]	Mean (median) % change from screening in total volume of 3 largest	-33.7 (-53.6)	-47.9 (-58.0)	-40.9 (-56.6)

Time point	Fibroid volume parameter	Ulipristal 5 mg group (n=228)	Ulipristal 10 mg group (n=223)	Total (n=451)
	myomas			
	% subjects with myoma volume reduction ≥ 25%	74.1	79.3	76.7
	% subjects with myoma volume reduction ≥ 50%	53.4	60.6	57.1
	% subjects with uterine volume reduction ≥ 25%	46.4	45.9	46.2
	% subjects with uterine volume reduction ≥ 50%	9.3	15.8	12.6
End of treatment course 4[b]	Mean (median) % change from screening in total volume of 3 largest myomas	-36.9 (-67.0)	-50.6 (-70.4)	-43.7 (-69.7)
	% subjects with myoma volume reduction ≥ 25%	78.1	80.5	79.3
	% subjects with myoma volume reduction ≥ 50%	63.8	71.1	67.4
	% subjects with uterine volume reduction ≥ 25%	44.0	47.9	45.9
	% subjects with uterine volume reduction ≥ 50%	15.5	23.0	19.2

[a] 10-18 days after start of menstruation following the end of treatment course 2

[b] 10-18 days after start of menstruation following the end of treatment course 4

- Other endpoints
    - **Pain** was assessed using the Visual Analogue Scale (VAS; over a recall period of 1 month). Pain was assessed at the start and end of each treatment course, with changes from baseline (start of treatment course 1) reported. At baseline, mean (median) pain

VAS scores were 39.7 (39.0) and 42.6 (43.0) for the 5 mg and 10 mg groups respectively (VAS > 40 = severe pain). At the end of treatment course 1, the mean (median) change from baseline in pain VAS score was -26.2 (-24.5) for the 5 mg group and -28.3 (-25.0) for the 10 mg group. A similar pattern of improvement was observed after each treatment course. Overall, the change from baseline in pain VAS score was of lower magnitude at the start of each treatment course than at the end of treatment course.

– There were no differences observed between treatment groups in the change from baseline in pain VAS scores during the study. Improvement in pain VAS was observed at the post-treatment follow up visit (visit 12; approximately 3 months after the end of treatment course 4). The mean (median) change from baseline in pain VAS was -14.9 (-16.0) and -18.2 (-19.0) for the 5 mg and 10 mg groups respectively.

– **Quality of life** was assessed by the UFS-QoL (Uterine Fibroid Symptoms questionnaire and EQ-5D questionnaire) at the start and end of each treatment course. Improvements in symptom severity were observed after treatment course 1 (mean [median] change from baseline of -32.30 (-34.38) and -31.19 (-31.25) in the 5 mg and 10 mg treatment groups respectively). Similar improvements in quality of life scores were observed with subsequent treatment courses; symptom severity scores approximating those in healthy women were observed after two treatment courses, and sustained up to the end of study assessment (visit 12). The changes in symptom severity score were similar between the two treatment groups throughout the study. Improvements from baseline in the EQ-50 score were also observed in both the 5 mg and 10 mg groups at the end of treatment courses 2 and 4.

– Eligibility for surgery was not an inclusion criterion for the study. The Sponsor states at the start of the study, there was no surgery planned for 90.9% of subjects. During the study surgery was performed for 16 (3.5%) of subjects, with surgery reported to not have been planned for 13 subjects. The Sponsor states the decision drivers for surgery were 'mainly Investigator driven (n=7), 'mainly driven by subject request' (n=6), and 'equal influence' (n=3).

A summary of the main findings is provided.

Evaluator comment:

The EMA Evaluator noted the sample size and statistical methods to be considered adequate. In particular, the duration of diary data required for this study did raise the concern regarding missing data, although the Sponsor did acknowledge this and pre-planned analyses to address missing data were considered acceptable by the EMA Evaluator. This evaluator agrees with same. Over the course of the study (from start of treatment course 1 to the end of study follow up visit), 25.3% of subjects discontinued (comparable between groups). Reasons for discontinuation were various, most commonly subject request (including lack of improvement, trial related reason) or adverse event. Compliance was acceptable (mean regimen compliance 99.4% and mean protocol compliance 88.2% [reflects early termination of subjects], similar between groups).

The proportion of subjects in amenorrhoea at the end of treatment course 4 (60.5% of subjects in the 10 mg group and 48.7% of subjects in the 5 mg group), was lower compared to the end of treatment course 2 (72.7% and 61.9% of subjects in 10 mg group and 5 mg group respectively). This Evaluator agrees with the EMA Evaluator's position that amenorrhoea as defined in this study (no more than 1 day of spotting in a 35 day interval) was a rather strict endpoint, particularly as the primary endpoint with respect to uterine bleeding in earlier short-term pivotal studies was a PBAC score of < 75. When taking other bleeding pattern endpoints into consideration, such as improvements in controlled bleeding and median time to amenorrhoea, the improvements in bleeding profile are considered clinically relevant.

A statistically significant difference in the 5 mg and 10 mg treatment groups for the primary endpoints, amenorrhoea at the end of the first two courses, and at the end of all 4 treatment courses, was demonstrated. However, given the similar results for both treatment groups with respect to other bleeding parameters (number of subjects in amenorrhoea at the end of each treatment course, controlled bleeding), reduction in uterine and myoma volume, and improved quality of life indicators, this Evaluator endorses the argument by the EMA Evaluator that the 5 mg dose is deemed adequate due to overall small differences.

7.1.2.   Study PGL09-027 (extension of Study PGL09-026)

PGL09-026 was a Phase III, multi-centre, open-label study to assess the efficacy and safety of UPA 10 mg once daily for 3 months in 209 pre-menopausal women with myomas and heavy uterine bleeding. The open-label phase was followed by a 10-day double-blind phase during which subjects were randomised in 1:1 ratio to treatment with progestin (norethisterone acetate; NETA) or placebo. The rationale for the short course progestin was to investigate the reversibility of progesterone receptor modulator associated endometrial changes (PAEC), and possibly schedule menstruation without counteracting beneficial effects of UPA on uterine myoma reduction.

There were 132 subjects who continued into Study PGL09-027, the optional open-label extension study to assess the sustained efficacy and safety of long-term on-off treatment with UPA (n=68 placebo group and n=64 NETA group).

Subjects received three successive courses of 3 months [90 days] of UPA 10 mg daily, with each course followed by a 10-day double-blinded treatment period with NETA (10 mg daily) or matching placebo. Following the double-blind treatment there was a drug free interval after each course, which included at least one menstrual bleed before the next cycle of UPA was commenced. The first dose of UPA was to be administered within the first 4 days of menstruation for treatment courses 1 and 2, and on the first day of menstruation for treatment courses 3 and 4.

The primary efficacy endpoint of both studies was the percentage of subjects in amenorrhoea (defined as no bleeding for longer than 35 days; one day of spotting within any 35 day interval was accepted) at the end of each UPA treatment course. Subjects recorded PBAC for the first 8 days of the first menstruation following each treatment cycle. Bleeding occurring outside this timeframe was recorded in the subject diary as spotting, bleeding or heavy bleeding. Secondary endpoints included assessment of myoma volume, pain and quality of life assessments.

7.1.2.1.   Primary endpoint (ITT population)

The percentage of subjects in amenorrhoea at the end of each treatment course (prior to NETA/placebo treatment) was:

- 79.5% (95% CI: 71.9%, 85.5%)) after treatment course 1 (those patients from Study PGL09-026 who continued into the extension study; n=105/132)
- 88.5% (95% CI: 82.0%, 92.9%) after treatment course 2 (n=116/131)
- 88.2% (95% CI: 81.2%, 92.9%) after treatment course 3 (n=105/119)
- 89.7% (95% CI: 82.5%, 94.2%) after treatment course 4 (n=96/107)

The results for key secondary efficacy endpoints were (ITT population):

- Uterine bleeding endpoint
  - The percentage of subjects in amenorrhoea at the end of treatment courses 1, 2, 3 and 4 was 72.0 % (95% CI: 62.8%, 79.6%).

- the mean (median) time to amenorrhoea (from first dose of UPA to start of amenorrhoea for each treatment course was:
  - 9.4 (4.0) days at the end of treatment course 1 (Study PGL09-026)
  - 3.3 (2.0) days at the end of treatment course 2
  - 5.3 (3.0) days at the end of treatment course 3
  - 4.2 (3.0) days at the end of treatment course 4

- Fibroid endpoints

Fibroid volume (total volume of 3 largest myomas as assessed by TVUS) was evaluated 2 weeks after menstruation following each treatment course and 10 day placebo/NETA for treatment courses 2 and 3, whilst at the end of the treatment (prior to NETA/placebo double blind treatment) for treatment course 1 and 4.

The following table summarises the results for all subjects (n=132) and the ulipristal /placebo subgroup (n=68) regarding fibroid volume assessment.

Table 8. Fibroid volume endpoints for each treatment course.

Time point	Fibroid Volume Parameter	Ulipristal + Placebo (n=68)	Total (n=132)
End of treatment course 1	Mean (median)% CFS in total fibroid volume	-42.7 (-48.5)	-41.9 (-49.9)
	Percentage (number) of subjects with ≥25% reduction in fibroid volume[a]	77.9 (53/68)	77.7 (101/130)
	Percentage (number) of subjects with ≥50% reduction in fibroid volume[a]	47.1 (32/68)	50.0 (65/130)
End of treatment course 2[b]	Mean (median)% CFS in total fibroid volume	- 51.3 % (-63.4%)	-43.7 % (-63.2%)
	Percentage (number) of subjects with ≥25% reduction in fibroid volume[a]	80.0 (48/60)	79.8 (95/119)
	Percentage (number) of subjects with ≥50% reduction in fibroid volume[a]	66.7 (40/60)	64.7 (77/119)
End of treatment course 3[b]	Mean (median)% CFS in total fibroid volume	- 52.0% (-66.5%)	-41.0% (-67.0%)
	Percentage (number) of subjects with ≥25% reduction in fibroid volume[a]	81.8 (45/55)	78.3 (83/106)
	Percentage (number) of subjects with ≥50%	65.5 (36/55)	62.3 (66/106)

Time point	Fibroid Volume Parameter	Ulipristal + Placebo (n=68)	Total (n=132)
	reduction in fibroid volume[a]		
End of treatment course 4	Mean (median)% CFS in total fibroid volume	-57.3% (-71.2%)	-53.5% (-72.1%)
	Percentage (number) of subjects with ≥25% reduction in fibroid volume[a]	84.0 (42/50)	82.3 (79/96)
	Percentage (number) of subjects with ≥50% reduction in fibroid volume[a]	66.0 (33/50)	69.8 (67/96)
Follow up visit (approximately 3 months after end of treatment)	Mean (median)% CFS in total fibroid volume	-42.7 (-59.3)	-33.7 (-58.8)
	Percentage (number) of subjects with ≥25% reduction in fibroid volume[a]	76.5 (39/51)	72.2 (70/97)
	Percentage (number) of subjects with ≥50% reduction in fibroid volume[a]	60.8 (31/51)	57.7 (56/97)

[a] Denominator for percentage is number of subjects with non-missing myoma volume reduction at each visit

[b] Assessment 2 weeks after menstruation following treatment course and placebo / NETA double blind period

- Other endpoints

- Improvements from baseline in all 3 components of the SF-MPQ were reported at the end of each of the UPA and NETA/placebo treatment courses. For the Part B component (VAS), the mean (median) change from baseline was -28.9 (-27.5) after treatment course 2, -27.9 (-25.0) after treatment course 3, and -32.1 (-30.5) after treatment course 4, with a sustained reduction in VAS score reported at the end-of- treatment visit (mean [median] change from baseline -20.4 [-17.0]).

- Improvement (decrease) from baseline in UFS-QoL symptom severity scores were reported at the end of each ulipristal and NETA/placebo treatment course (mean [median] change from baseline of -30.53 [-34.38], -27.73 [-25.00], -29.95 [-28.13] after treatment courses 2, 3 and 4 respectively), with UFS-QoL scores reported as being comparable to those of healthy women at the end-of-treatment follow up visit.

- The EMA Evaluator has provided a table with key efficacy points for the two long-term studies PGL11-006 and PGL09-027.

  Evaluator comment: This study comprised 132 patients, of which 75% completed the study. Discontinuations were evenly balanced across both the placebo and NETA groups, with no trend for discontinuation observed by this Evaluator or the EMA evaluator. Mean UPA tablet regimen compliance was 99.1% (mean UPA tablet protocol compliance 92.1%, stated to reflect early termination of subjects prior to visit D).

The primary endpoint was assessed prior to the use of NETA, as was the time to amenorrhoea. A comparison of these findings with those of Study PGL11-006 is provided below.

Table 9. A comparison of the main study endpoints for Study PGL11-006 (FAS 1 population) and PGL09-027 (ITT Population).

Parameter	Treatment Course	PGL11-006 UPA 5 mg (n=228)	PGL11-006 UPA 10 mg (n=223)	PGL09-027 UPA 10 mg (n=132)
% Subjects in amenorrhoea at end of treatment course [n]	1 and 2	61.9 (122/197)	72.7 (136/187)	76.3 (100/131)
	1, 2, 3 and 4	48.7 (95/195)	60.5 (112/185)	72.0 (77/107)
Mean (median) time to amenorrhoea (day)	End of course 2	Median 5.0	6.0	2.0
	End of course 4	5.0	5.0	3.0
Median change from screening in PBAC score first menses post treatment*	Post course 2	-95.0	-109.5	-127.0 (n=65)
	Post course 4	-118.0	-121.0	- 97.0 (n=49)

* Results are presented for the PGL/placebo group only, as NETA had a positive effect on the reduction of menstrual bleeding.

For the primary endpoint, the percentage of subjects in amenorrhea was higher in the 10 mg group in both PGL09-027 and PGL11-006, compared with those in the 5 mg group in Study PGL11-006.

7.2. Other efficacy studies

7.2.1. Study PGL07-021

Study PGL07-021 was a Phase III, randomised double-blind, placebo-controlled, parallel-group, multi-centre study to assess the efficacy and safety of UPA vs. placebo for the pre-operative treatment of symptomatic uterine myomas. The study population comprised 242 pre-menopausal women with symptomatic uterine myomas, excessive uterine bleeding and anaemia for whom a surgical procedure was indicated to treat the myomas.

In Part A of the study, 242 participants were randomised in a 2:2:1 ratio to receive UPA 5 mg once daily (n=96), UPA 10 mg once daily (n=98) or matching placebo (n=48) for 13 weeks, after which those subjects still qualifying for surgery underwent a surgical procedure as determined by the investigator. All patients received concomitant oral iron therapy (80 mg once daily) from baseline until the week 13 visit. Subjects completed the PBAC daily during the 13 week treatment period (from Day 1 of menstruation to the end of treatment). There were 224

subjects who continued into Part B of the study, where subjects were followed up at 3 and 6 months post treatment (at week 26 and week 38).

The co- primary efficacy endpoints were:

- Percentage of subjects with reduction in uterine bleeding (defined as a PBAC score <75 at end-of-treatment visit (week 13).

- Change in total myoma volume (assessed by MRI) from screening to end-of-treatment visit (week 13).

Key findings from Part A were:

7.2.1.1. Primary endpoints (ITT population)

- Mean (median) PBAC scores at baseline were similar across the 3 groups (5 mg = 487 [386], 10 mg = 411 [330], placebo = 460 [376]).

- The percentage of patients with a PBAC score of < 75 at week 13 were:

    - 91.5% in the 5 mg group.

    - 92.5% in the 10 mg group.

    - 18.8% in the placebo group.

- The difference in the percentage of subjects (UPA vs. control) with PBAC score < 75 was 72.7% (95% CI: 55.1, 83.2; p < 0.001) and 73.7% (95% CI: 56.2, 84.0; p < 0.001) for the 5 mg and 10 mg groups, respectively.

- The mean (median) percentage change in total fibroid volume from screening to week 13 was -14.7% (-21.2%) for the 5 mg group, -16.0% (-12.3%) for the 10 mg group and 0.9% (3.0%) for the placebo group.

- The difference (UPA vs. placebo) in percentage change in total fibroid volume from screening was statistically significant for both groups: -22.6 % (95% CI: -36.1, -8.2; p=0.002) for the 5 mg group and -18.2 % (95% CI: -33.0, -5.2; p=0.006) for the 10 mg group.

The results for key secondary endpoints were (ITT population):

- The percentage of subjects in amenorrhoea (defined as being present if a subject had a PBAC score of ≤2 [minor spotting] over 28 days) at week 13 was higher in both UPA groups (73.4% 5 mg, 81.7% 10 mg) than placebo (6.3%). For both the 5 mg and 10 mg groups, the difference from placebo was statistically significant.

- The percentage of patients with a total myoma volume reduction of ≥ 25% was 17.8% for placebo, 41.2% for the 5 mg group and 41.3% for the 10 mg group. The difference (UPA vs. placebo) was statistically significant for the 5 mg group (p=0.014) and the 10 mg group (p=0.014).

- There were a higher percentage of subjects in the UPA groups with a reduction in uterine volume of ≥ 25% in the 5 mg group (34.1%) and 10 mg group (28.2%) than the placebo group (6.4%). The difference for each treatment group vs. placebo was statistically significant.

- All treatment groups experienced a reduction in pain levels (as per the SF-MPQ) at week 13, with a statistically significant effect observed in the 10 mg group (vs. placebo) for the Part A score [p=0.037]).

- Statistically significant improvements from baseline in haemoglobin and haematocrit were observed for both ulipristal groups (compared to placebo) at week 5, week 9 and week 13.

- Surgery cancellation at the end of Part A of the study was highest for the placebo group (72.9%, compared with 65.6% in the 5 mg and 61.7% in the 10 mg group).

  Evaluator comment: This trend was observed at the 6 month post treatment follow up (week 38), with 60.4% of placebo subjects, 54.7% in 5 mg and 47.9% in the 10 mg group not having surgery. The Sponsor states a strong centre effect was present, with nearly all subjects in some centres having surgery vs. very few in others, regardless of treatment group assignment. Although eligibility for surgery was requirement for the trial, desire for fertility preservation, differences in both individual investigator and subject's decision for surgery are cited by the Sponsor as potential influencing factors in some centres.

7.2.2.   Study PGL07-022

Study PGL07-022 was a Phase III, randomised, multi-centre, parallel-group, double-blind, double-dummy, active-comparator controlled study to assess the efficacy and safety of UPA vs. the GnRH agonist leuprorelin for the pre-operative treatment of symptomatic uterine myomas. The primary objective of the study was to demonstrate non-inferior efficacy of UPA vs. GnRH in the reduction of excessive uterine bleeding due to uterine myomas prior to surgery.

In Australia, leuprorelin is not registered for use in the management of uterine fibroids. The GnRH agonist goserelin 3.6 mg is registered for use in uterine fibroids. The Sponsor states "*the two GnRH agonists being similar, the active comparator selected in the study PGL07-022 and study findings are thus appropriate to conclude about the benefit of Esmya over medical therapies currently registered in Australia to manage uterine fibroids.*"

The study will be discussed in brief with a focus on relevant findings.

The study population consisted of 307 pre-menopausal women with symptomatic uterine myomas, and excessive uterine bleeding for whom a surgical procedure was indicated. Participants were randomised in a 1:1:1 ratio to receive one of the following treatments:

- UPA 5 mg orally (daily) and IMI saline solution (once monthly) (n=102)

- UPA 10 mg orally (daily) and IMI saline solution (once monthly) (n=103)

- UPA matching placebo orally (daily) and IMI leuprorelin 3.75 mg (once monthly) (n=102).

Study participants were treated for 13 weeks after which those subjects still eligible for surgery underwent a surgical procedure as determined by the Investigator. The primary efficacy endpoint was the percentage of subjects with reduction in uterine bleeding (defined as PBAC < 75) at the week 13 end-of-treatment visit (PP population). The primary endpoint was assessed using a pre-specified non-inferiority margin of 20%; the Sponsor states this was based on consultation with clinical experts in the field.

The key findings were (PP population):

- The percentage of patients with a PBAC score of < 75 was 90.3%, 97.9% and 89.1%, for the UPA 5 mg, UPA 10 mg and leuprorelin groups respectively.

- the 2.5% lower confidence limit for UPA 5 mg – leuprorelin, and UPA 10 mg – leuprorelin, was -9.3% and 0.4%, both well within the pre-specified non-inferiority margin of -20%.

- there was a reduction in the volume of the 3 largest fibroids in all three treatment groups, with mean (median) change from baseline of -36.7 (-42.1) %, -42.0 (-53.5) % and -27.4 (-35.6) %, for the UPA 5 mg, UPA 10 mg and leuprorelin groups respectively. There were no statistical significant differences between either of the UPA groups and leuprorelin.

- at week 13, there were 77.8% in the UPA 5 mg group and 89.0% of subjects in the UPA 10 mg group in amenorrhoea (defined as PBAC score ≤ 2).

A summary of other secondary efficacy endpoints is provided in EMA Report 1 page 63.

7.2.3. Study PGL09-026

As discussed above, PGL09-026 was a Phase III, multi-centre, open-label study to assess the efficacy and safety of ulipristal 10 mg once daily for 3 months in 209 pre-menopausal women with myomas and heavy uterine bleeding. The open-label phase was followed by a 10-day double-blind phase during which subjects were randomised in 1:1 ratio to treatment with NETA or placebo.

The primary efficacy endpoint of the study was the percentage of subjects in amenorrhoea (defined as no bleeding for longer than 35 days; one day of spotting within any 35 day interval was accepted) at the end of ulipristal 10 mg treatment.

The key findings were (ITT population):

- there were 78.5% subjects in amenorrhoea at the end of treatment

- the mean (median) time to amenorrhoea was 10.6 (5.0) days.

- the mean (median) % change from screening in total volume of the 3 largest myomas (assessed at the end of treatment and prior to double blind NETA/placebo period) for the total population (n=201) was -38.9 (-45.3)%.

7.2.4. Phase II Studies PGL-N-0287 and PGL-N-0090

Studies PGL-N-0287 and PGL-N-0090 were dose response studies. Study PGL-N-0287 was a Phase II randomised double-blind, placebo-controlled, parallel group study, to compare the effect of daily administration of UPA (10 mg or 20mg) vs. placebo on uterine fibroid size in healthy women aged 33-50 with symptomatic fibroids desiring hysterectomy. There were 22 subjects, who were randomised to receive UPA 10 mg, UPA 20 mg or placebo, for 3 menstrual cycles. The primary efficacy variable was absolute change in uterine fibroid size as determined by MRI.

The Sponsor states subject recruitment was difficult due to mandatory hysterectomy at the end of trial; sample size was 40% of planned (n=7, 6, 6 in the 10 mg, 20 mg and placebo groups respectively). Further, there was considerable heterogeneity in uterine fibroid size at baseline. This Evaluator agrees with the EMA Evaluator's conclusions "*the number of patients included was considered too small and the variability in fibroid volume is too large to allow conclusions of efficacy and of a dose response relationship. However, the data appear to support an effect of UA in reducing fibroid volume*".

Study PGL-N-0090 was a Phase II randomised double-blind, placebo-controlled, parallel group study, to compare the effect of daily administration of UPA (10 mg or 20mg) in 38 healthy cycling women with symptomatic leiomyomata. The study consisted of 2 phases, each for 3 menstrual cycles (or up to 102 days). During Phase 1, women were randomised to receive placebo, UPA 10 mg or UPA 20 mg. Phase 2 was an optional extension, during which women chose to either continue treatment for a further 3 months or undergo surgical treatment. The primary outcome measure was the absolute change in fibroid size as determined by MRI.

There were 38 subjects completing Phase 1, with the majority electing to undergo surgery (n=23). At the end of Phase 1, total uterine fibroid volume decreased from baseline in both UPA groups (mean [SD] decrease of 15.5 [21.7] % in the 10 mg group and 19.1 [19.2] % in the 20 mg group), whilst in the placebo group, mean total uterine fibroid volume increased by 11.0 (29.4) %

There were too few subjects in Phase 2 to draw any meaningful conclusion (n=9).

7.3. Analyses performed across trials (pooled & meta analyses)

Nil provided.

7.4. Evaluator's conclusions on clinical efficacy

Data for up to 4 repeated treatment courses with UPA has been provided in the long-term study PGL11-006, as well as Study PGL09-027. The EMA Evaluator noted the inclusion and exclusion criteria for Study PGL11-006 were acceptable and generally consistent with those of previous studies, except that eligibility for surgery was not a requirement.

Demographics were similar across the Phase III trials, with the patient population mostly white, of child-bearing potential and aged approximately 40; these demographic parameters are considered largely consistent with the target therapeutic population in Australia.

This Evaluator agrees with the EMA Evaluator the efficacy endpoints used in the clinical trials were clinically relevant (assessment of bleeding, myoma volume, pain and quality of life assessments). There were differences observed between the 5 mg group and 10 mg ulipristal groups for the primary endpoint (percentage of subjects in amenorrhoea) in the pivotal Study PGL11-006, although this was considered a rather strict endpoint as discussed in the Evaluator comments (page 20). When taking into consideration other bleeding pattern endpoints, such as controlled bleeding (no episodes of heavy bleeding and maximum 8 days if bleeding over 56 days) and the median time to amenorrhoea, the results between the 5 mg and 10 mg UPA groups were similar. Sustained improvements in bleeding pattern profile endpoints were evident after consecutive courses of UPA.

Additional supportive evidence was provided in the short-term studies, with over 90% of subjects in the ulipristal groups with PBAC scores < 75 (considered consistent with normal menstrual blood loss) after a single treatment course. Further proof of efficacy was demonstrated by reduction in fibroid volume, uterine volume as well as improvement in pain and quality of life assessment scores, which were maintained with repeat treatment courses in the long-term studies. The results for these parameters were generally similar between the 5 mg and 10 mg UPA groups. Statistically significant improvement over placebo was noted in the short-term study PGL07-021 for the co-primary endpoints (for reduction in uterine bleeding and change in total myoma volume). There are no long-term comparator products available, and the active comparator used in the short-term study is not registered for use in fibroids in Australia.

8. Clinical safety

8.1. Studies providing evaluable safety data

There are safety data for UPA available from the 5 Phase III Studies:

- 2 long-term studies – PGL11-006 and PGL09-027.

- 3 short-term studies – PGL07-021, PGL07-022 and PGL07-026.

Further, safety data are available from 2 Phase II studies (PGL-087 and 0090), as well as 28 studies conducted in healthy female subjects as part of the development program for emergency contraception. Additional safety data has been evaluated in the original marketing authorisation application for UPA 30 mg (EllaOne).

8.1.1. Pivotal efficacy studies

In the pivotal efficacy studies, the following safety data were collected:

- General adverse events (AEs)

- AEs of special interest (AESI), including reproductive and breast disorders, endometrial safety.

- Laboratory tests, including endocrine parameters

8.2. Patient exposure

The Sponsor states there have been over 6200 subjects exposed to ulipristal during the clinical development program (as emergency contraception and as a treatment for uterine fibroids). In particular, 6168 subjects have been exposed to a dose of UPA ≥ 5 mg or above (any duration), 4999 subjects received a single dose, and 1238 subjects have received repeated doses of UPA.

Of the 1238 subjects receiving multiple doses of UPA:

- 1053 have been exposed to dose of UPA ≥ 5 mg for ≥ 3 months.

- 551 have been exposed to dose of UPA ≥ 5 mg for ≥ two 3 month courses (stated to equate to 9 months when including off treatment intervals).

- 457 have been exposed to UPA 5 mg or 10 mg for four 3 month courses (stated to equate to 21 months when including off treatment intervals).

Table 10. Phase III repeated-dose studies with ulipristal acetate in subjects with symptomatic uterine fibroids (safety population).

Study	Design	Ulipristal acetate 5 mg/day	Ulipristal acetate 10 mg/day	Control Placebo	Control Active control	Planned Duration of treatment	Overall treatment + follow-up period
		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,e]	Approx. 12 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.

[e] Study PGL11-006 comprises a total of four 3-month treatment courses: at time of preparation of this summary, 369 and 271 subjects have completed 3 and 4 treatment courses respectively.

8.3. Adverse events

8.3.1. All adverse events (irrespective of relationship to study treatment)

8.3.1.1. Study PGL11-006

Treatment emergent adverse events (TEAEs) were considered either:

- On-treatment – if the start date was on or after the first dose of study drug within each treatment course an up to 7 days after the last dose of study drug within each treatment course.

- Off-treatment - if the start date was more than 7 days after the last dose of study drug within each treatment course and prior to the start of the next treatment course.

Table 11 below provides a summary of the adverse event data for Study PGL11-006.

Table 11. Summary of the adverse event data for Study PGL11-006 (Safety Set).

	Ulipristal treatment course 1			Ulipristal treatment course 2		
	5 mg (n=230)	10 mg (n=221)	Total (n=451)	5 mg (n=230)	10 mg (n=221)	Total (n=451)
TEAEs	102 (44.3%)	98 (44.3%)	200 (44.3%)	59 (27.4%)	60 (29.3%)	119 (28.3%)
TEAEs considered related to study medication	47 (20.4%)	43 (19.5%)	90 (20.4%)	28 (13.0%)	22 (10.7%)	50 (11.9%)
SAEs	3	3	6 (1.3%)	1	2	3
AESI	1	1	2 (0.4%)	0	1	3
	Ulipristal treatment course 3			Ulipristal treatment course 4		
	5 mg (n=230)	10 mg (n=221)	Total (n=451)	5 mg (n=230)	10 mg (n=221)	Total (n= 451)
TEAEs	32 (16.6%)	38 (20.2%)	70 (18.4%)	43 (23.9%)	33 (19.0%)	76 (21.5%)
TEAEs considered related to study medication	9 (4.7%)	12 (6.4%)	21 (5.5%)	11 (6.1)	14 (8.0%)	25 (7.1%)
SAEs	5 (2.6%)	1	6 (1.6%)	1	2	3
AESI	0	1	0	0	0	0

- On-treatment TEAEs were reported by 57.6% subjects overall (56.1% in 5 mg group and 59.3% in 10 mg group). The majority (97.6%) were considered mild or moderate in intensity. AEs were reported most frequently in the SOCs infections and infestations (22.0%), reproductive and breast disorders (21.1%) and nervous system disorders (16.6%).

- For each treatment course, on-treatment TEAEs were reported by:

- 44.3% subjects in each group during treatment course 1.

- 27.4% subjects (5 mg group) and 29.3% subjects (10 mg group) during treatment course 2.

- 16.6% (5 mg group) and 20.2% subjects (10 mg group) during treatment course 3.

- 23.9% subjects (5 mg group) and 19.0% (10 mg group) during treatment course 4.

- Off-treatment TEAEs were reported by 36.6% subjects overall (37.4% in 5 mg group and 35.7% in 10 mg group). Again the majority of TEAEs were considered mild or moderate in intensity (95.7%).

- For each treatment course, off -treatment TEAEs were reported by:

- 16.5% (5 mg group) and 19.0% (10 mg group) subjects following treatment course 1.

- 14.4% (5 mg group) and 11.7% (10 mg group) subjects following treatment course 2.

- 14.5% (5 mg group) and 11.7% (10 mg group) subjects following treatment course 3.

- 18.9% (5 mg group) and 19.5% (10 mg group) subjects following treatment course 4.

- The most frequent on-treatment TEAEs were headache (13.5%), hot flush (9.1%), influenza (4.9%), nasopharyngitis (4.0%) and breast pain/tenderness/discomfort (4.0%).

- Overall there were more TEAEs reported during treatment course 1 than treatment courses 2, 3 and 4, with the number of subjects reporting on-treatment TEAEs comparable between the 5 mg and 10 mg groups.

- The most frequent off-treatment TEAEs were headache (4.7%), dysmenorrhoea (4.4%) and menorrhagia (3.1%)

8.3.1.2.   Study PGL09-027

- Open-label TEAEs were defined as those with a start date on or after the first dose of UPA (in each treatment course) and before the first dose of double-blind medication (NETA or placebo), or, if double-blind medication was never started, up to and including 7 days after the last dose of UPA.

- Open-label TEAEs were reported by 68.9 % subjects overall. The majority (97.3%) were considered mild or moderate in intensity.

- For each treatment course, open-label TEAEs were reported by:

- 55.3% subjects during treatment course 1 (Study PGL09-026)

- 20.6% subjects during treatment course 2

- 29.4% subjects during treatment course 3

- 34.6% subjects during treatment course 4.

- The most frequent open-label TEAEs overall were headache (19.7%), nasopharyngitis (13.6%), hot flush (9.1%), nausea (6.1%), back pain (6.1%) and fatigue (6.1%).

8.3.1.3.   Study PGL07-021

- TEAEs were reported for 49.5% subjects in 5 mg group, 53.1% in 10 mg group and 45.8% in the placebo group.

- The most common TEAEs reported were headache (4.2% in 5 mg group, 10.2% in 10 mg group, 4.2% placebo), breast pain/tenderness/discomfort (2.1% in the 5 mg group, 6.1% in the 10 mg group, 0% placebo group).

8.3.1.4.   Study PGL07-022

- TEAEs were reported for 77.3% subjects in 5 mg group, 76.7% in the 10 mg group and 84.2% in the leuprorelin group.

- The most common TEAEs reported were hot flush (25.8% in the 5 mg group, 24.3% in the 10 mg group), and headache (25.8% in the 5 mg group, 18.4% in the 10 mg group).

8.3.1.5.   Study PGL09-026

- Open-label TEAEs were defined as those with a start date on or after the first dose of ulipristal (in each treatment course) and before the first dose of double-blind medication (NETA or placebo), or, if double-blind medication was never started, up to and including 7 days after the last dose of ulipristal.

- Open-label TEAEs were reported by 57% subjects; most commonly, headache (16.3%), nasopharyngitis (6.7%) and hot flush (4.8%).

8.3.2.   Treatment-related adverse events (adverse drug reactions)

8.3.2.1.   Study PGL11-006

There were 123 (27.3%) subjects who experienced at least one on-treatment TEAE considered related to study medication (27.0% in the 5 mg group and 27.6% in the 10 mg group).

For each treatment course, on-treatment TEAEs considered related to study medication were reported for:

- 20.0% subjects during treatment course 1.

- 11.9% subjects during treatment course 2.

- 5.5% subjects during treatment course 3.

- 7.1% subjects during treatment course 4.

The most commonly reported treatment-related TEAEs were hot flush (8.9%) and headache (5.5%). The majority of events of hot flush and headache were considered mild or moderate in intensity. There were 2 treatment-related TEAEs considered SAEs, both reported during treatment course 4 (bipolar disorder for 1 subject in the 5 mg group and uterine leiomyomata for 1 subject in the 10 mg group).

There were 27 (6.0%) subjects who experienced at least one off-treatment TEAE considered related to study medication (7.0% in the 5 mg group and 5.0% in the 10 mg group). The most common reported treatment-related off-treatment TEAEs were menorrhagia (1.1%) and endometrial hyperplasia (0.9%). The majority of events were single events across a variety of SOCs.

8.3.2.2.   Study PGL09-027

- For each treatment course, open-label TEAEs considered related to study medication were reported for:
  - 27.3% subjects during treatment course 1.
  - 3.8% subjects during treatment course 2.
  - 12.6% subjects during treatment course 3.
  - 6.5% subjects during treatment course 4.

- The most commonly reported treatment-related open-label TEAEs were: headache (8.3%), hot flush (8.3%), acne, alopecia and breast pain/discomfort/tenderness (3.0% each).

8.3.2.3. Study PGL07-021

Treatment-related TEAEs were reported for 22.4% (10 mg group), 18.9% in the 5 mg group and 8.3% placebo, most commonly headache (3.1% 10 mg group, 1.1% 5 mg group) and breast pain (2.0% 10 mg group, 2.1% 5 mg group).

8.3.2.4. Study PGL07-022

Treatment-related TEAEs were reported for 51.5% (10 mg group) and 58.8% in the 5 mg group. The most common treatment-related TEAEs were hot flush (24.3% 10 mg group, 24.7% 5 mg group) and headache (5.8% 10 mg group, 15.5% 5 mg group).

8.3.2.5. Study PGL09-026

Open-label treatment-related TEAEs were reported for 29.7% subjects, most commonly headache (7.7%), hot flush (4.3%) and breast discomfort /pain/tenderness (3.8%).

8.3.3. Deaths and other serious adverse events

8.3.3.1. Study PGL11-006

There were 2 deaths during the study (n=1 accidental death and n=1 homicide), neither of which were considered study medication related.

On-treatment SAEs were reported for 16 (3.5%) subjects, comparable between the 5 mg and 10 mg groups. The majority of events occurred once. Two SAEs were considered study-drug related as noted above. Off-treatment SAEs were reported for 13 (2.9%) subjects.

8.3.3.2. Study PGL09-027

There were no deaths reported. SAEs were reported for 6 subjects during open-label treatment; 2 were considered related to ulipristal (n=1 metrorrhagia and n=1 heavy uterine bleeding).

8.3.3.3. Other studies

There were no deaths reported in Study PGL07-021, Study PGL07-022 or Study PGL09-026.

There were 5 subjects with SAEs in Study PGL07-021 during the treatment period, none of which were considered related to study medication by the Investigator (uterine leiomyoma, breast cancer in placebo group, uterine haemorrhage and ovarian haemorrhage in the 5 mg group, uterine haemorrhage in 10 mg group).

In Study PGL07-022, SAEs were reported for 5 subjects in the 5 mg group (headache, thyroid cancer, sarcoma, operative haemorrhage, post-procedural complication) and 4 subjects in the 10 mg group (uterine polyp, haemangioma, leiomyoma and uterine haemorrhage; the latter 2 SAEs were considered study drug related by the Investigator).

There were no SAEs during open-label treatment in Study PGL09-026.

8.3.4. Discontinuation due to adverse events

8.3.4.1. Study PGL11-006

Discontinuations due to TEAEs were reported for 32 (7.1%) of subjects (7.0% in the 5 mg group and 7.2% in the 10 mg group). Generally, study discontinuations due to TEAEs were reported for a variety of PTs.

8.3.4.2. Study PGL09-027

There were 6 subjects with open-label TEAEs leading to study discontinuation: leg pain during treatment course 2, heavy uterine bleeding during treatment course 2, metrorrhagia during treatment course 3, abdominal pain/constipation/dyspepsia/vertigo during treatment course 3 heavy uterine bleeding during treatment course 4 and blood pressure increased during treatment course 4.

8.3.4.3. Study PGL07-021

Three subjects discontinued due to TEAEs (endometrial hyperplasia [5 mg group; the Sponsor states this slide was re-assessed as PAEC], ovarian cyst [10 mg group], and breast cancer [placebo]).

8.3.4.4. Study PGL07-022

There were 9 subjects with TEAEs leading to discontinuation in Study PGL07-022 (n=1 in the 5 mg group (uterine sarcoma not considered study drug related], n=2 in the 10 mg group [insomnia, hand tremor/anxiety in 1 subject and uterine bleeding in another], n=6 leuprorelin).

8.3.4.5. Study PGL079-026

There was 1 subject with a TEAE which led to discontinuation (headache).

8.3.5. Adverse events of special interest

8.3.5.1. Reproductive and breast disorders

Study PGL11-006

- On-treatment TEAEs from the reproductive and breast disorders SOC were reported for 21.5% subjects overall in the study, and for:
  - 13.5% (5 mg group) and 13.6% (10 mg group) during treatment course 1.
  - 7.9% (5 mg group) and 6.8% (10 mg group) during treatment course 2.
  - 4.7% (5 mg group) and 8.0% (10 mg group) during treatment course 3.
  - 7.8% (5 mg group) and 6.9% (10 mg group) during treatment course 4.

- The most frequent reported on-treatment TEAE was hot flush (9.1%), followed by breast discomfort/tenderness/pain (4.0%).

- The EMA Evaluator noted there was no increase in castration-related symptoms (including hot flush, depression, decreased libido and vaginal infection) with repeated courses of UPA.

- Breast pain/discomfort/ tenderness was most frequent during treatment course 1, reported by < 1% subjects in subsequent treatment courses.

- TEAEs related to excessive uterine bleeding were reported by:
  - 3.5% (5 mg group) and 1.8% (10 mg group) during treatment course 1.
  - 3.2% subjects in 5 mg group and 2.0% subjects in the 10 mg group after treatment course 2.
  - The Sponsor is asked to provide this data for treatment courses 3 and 4 (see Clinical Questions).

- The presence of ovarian cysts was assessed by TVUS at screening, and visits 6-12 inclusive (see table of scheduled visits below). The Sponsor states normal ovaries were observed for > 87% of subjects at all visits (noting for 3.6-6.3% subjects ovaries could not be assessed at a particular visit). There were a total of 9 subjects with the TEAE of ovarian cyst during the study; n=4 in the 5 mg group, and n=5 from the 10 mg group (n=1 in each group considered related to study medication).

- Return to menstruation was reported for 100%, 99.0%, 99.5% and 100% of subjects after treatment course 1, 2, 3 and 4 respectively. The mean (median) time to return to menstruation following discontinuation of medication was:
  - 26.2 (25.0) days after treatment course 1.
  - 29.3 (27.0) days after treatment course 2.

- 29.9 (28.0) days after treatment course 3.

- 30.5 (28.0) days after treatment course 4.

Study PGL09-027

- Open-label TEAEs from the reproductive and breast disorders SOC were reported for more subjects during treatment course 1 (19.7%) than in subsequent treatment courses:

  - 3.8% during treatment course 2.

  - 9.2% during treatment course 3.

  - 5.6% during treatment course 4.

- Hot flush was the most reported open-label TEAE reported (5.3% during treatment course 1, 0.8% during treatment course 2, 4.2% during treatment course 3 and 0.9% during treatment course 4). Other castration-related TEAEs occurred in n=3 subjects (depressed mood, loss of libido), with the EMA Evaluator again noting no increase in castration-related TEAEs with repeated UPA treatment courses (See EMA Report 2).

- There were 2 subjects with open-label TEAEs of excessive uterine bleeding (during treatment course 2, and 1 subject in treatment course 3 and 4), and 1 subject during the off-treatment period.

- The Sponsor states the number of subjects with ovarian cysts at each visits varied throughout the study. The majority were < 30 mm, and no trend of increasing number was observed with repeat treatment courses. There was 1 subject with an open-label TEAE of ovarian cyst (during treatment course 4).

- For the UPA/placebo group, the mean (median) time to return to menstruation following discontinuation of UPA was:

  - 24.9 (25.0) days after treatment course 1 (Study PGL09-026).

  - 28.2 (26.0) days after treatment course 2.

  - 32.6 (30.0) days after treatment course 3.

  - 33.2 (30.0) days after treatment course 4.

Study PGL07-021

- 14.7% and 14.3% subjects in the 5 mg group 10 mg group respectively reported TEAEs from the reproductive and breast disorders SOC.

- The most common reported TEAE was breast tenderness/pain/discomfort (2.1% in the 5 mg group and 6.0% in the 10 mg group), followed by hot flush (2.1% in the 5 mg group and 2.0% in the 10 mg group).

- Uterine haemorrhage was reported for 1 (1.1%) subject in the 5 mg group and 2 (2.0%) subjects in the 10 mg group.

- The presence of ovarian cysts was assessed by US at screening and by MRI at week 13 (with additional US at weeks 26 and 38 if abnormalities detected). There were 7 subjects with ovarian cysts present at screening only, 2 subjects with ovarian cysts at screening and week 13 (n=1 in each ulipristal group), 5 subjects with cysts at week 17 (n=2 in the 5 mg group and n=3 in the 10 mg group). There were 3 subjects with cysts present in the post-treatment period only (week 26 and week 38; all in the 10 mg group). There were 2 subjects reporting ovarian cysts as TEAEs (both in the 10 mg group).

- 99% and 95% of subjects in the 5 mg and 10 mg groups respectively had return to menstruation by week 38. Subjects who received ulipristal returned to menstruation after a mean duration of 27-33 days.

Study PGL07-022

- TEAEs from the reproductive and breast disorders SOC were reported for 40.2% subjects in the 5 mg group and 42.7% subjects in the 10 mg group.

- hot flush was the most reported TEAE reported (25.8% and 24.3% in the 5 mg and 10 mg groups respectively), followed by dysmenorrhoea (4.1% in the 5 mg group and 4.9% in the 10 mg group).

- genital haemorrhage was reported for 2 subjects each in the 5 mg and 10 mg groups, and metrorrhagia for 1 subject in each group.

- There was 1 subject with ovarian cysts present at screening and week 13 only (in 10 mg group), and 7 subjects with ovarian cysts present at week 13 only (n=3 in the 5 mg group and n=4 in the 10 mg group). Ovarian cysts were reported as TEAEs by 2 subjects in the 5 mg group (n=1 considered treatment related) and 7 subjects in the 10 mg group (n=4 considered treatment related).

- 100% and 97% of subjects in the 5 mg and 10 mg groups respectively had return to menstruation by week 38. Subjects who received ulipristal returned to menstruation after a mean duration of 31 to 34 days.

Study PGL09-026

- TEAEs from the reproductive and breast disorders SOC were reported for 18.7% subjects, most commonly hot flush (4.8%), followed by pelvic pain and breast discomfort (3.8% each).

- There were 4 subjects with TEAEs related to excessive uterine bleeding during the open-label phase (n=1 uterine haemorrhage, n=3 vaginal haemorrhage), and 4 subjects in the post-treatment period (n=1 each with uterine haemorrhage, vaginal haemorrhage and menometrorrhagia).

- The frequency of ovarian cysts increased at week 13 (n=12 subjects), although the EMA Evaluator noted there were no ovarian cysts of clinical significance reported at any time, with most cysts observed at a single evaluation only.

- return to menstruation was reported for 99.0% of subjects; the mean (median) time to return to menstruation for the UPA/placebo group was 25.5 (25.0) days (20.5 [17.5] days for total population)

8.3.5.2. *Endometrial safety*

Endometrial thickness

The Sponsor states the following regarding endometrial thickness:

> *Endometrial thickness varies considerably throughout the menstrual cycle in women of reproductive age. There is no agreement on the upper level of normal endometrial thickness in premenopausal women. However the American College of Radiology Guideline on abnormal vaginal bleeding states that for premenopausal women with bleeding, a thickness > 16mm has a sensitivity of 67%, a specificity of 75%, and a positive predictive value of 14% for demonstrating relevant pathology (Fleischer AC et al. 2007).*

The following table provides a summary of the visits/time points referred to in the discussion regarding endometrial safety in the Phase III studies:

Table 12. Study Visits for PGL09-026/PGL09-027 and PGL11-006.

Visit	PGL07-021 (Parts A and B)	PGL07-022 (Parts A and B)	PGL09-026/ PGL09-027 extension	PGL11-006 (Parts I and II)
Screening	Screening (*Biopsy*)		Screening (*Biopsy*)	Screening 1
				Screening 2
				Screening 3 (*Biopsy*)
Baseline (prior to drug administration)	Visit 2		Visit 2	Visit 2
Month 1	Week 5 (Day 29)		Visit 3	Visit 3
Month 2	Week 9 (Day 57)		Visit 4	Visit 4
Month 3 (End of treatment course 1)	Week 13 (end of treatment, assessment prior to surgery *Biopsy*)		Visit 5	Visit 5
Visit after treatment	Week 17 (end of Part A)		-	
Visit after treatment	*Week 26 (Part B: follow-up)*			
Visit after treatment	*Week 38 (Part B: follow-up Biopsy)*			
After treatment Course 1 (10-18 days after menses)	-		Visit 6 (*Biopsy*)	Visit 6
Start of treatment course 2			Visit A (end of Study PGL09-026, Start of PGL09-027)	-
End of treatment course 2			-	Visit 7
After treatment Course 2 (10-18 days after menses)			Visit B	Visit 8 (**End of Part I**) (*Biopsy*)
After treatment Course 3 (10-18 days after menses)			Visit C	Visit 9
End of treatment course 4			Visit D	Visit 10
After treatment Course 4 (10-18 days after menses)			Visit E (*Biopsy*)	Visit 11 (*Biopsy*)
Follow-up (approximately 3 months after last dose)			Visit F (*Biopsy*, if applicable)	Visit 12 (*Biopsy*)

Study PGL11-006

Endometrial thickness was measured with US at screening and visits 6-12 inclusive.

Mean endometrial thickness was similar between groups at baseline (8.4 mm both groups), with 4.9% subjects having endometrial thickness > 16mm.

Visits 6, 8, 9 and 11 occurred 10-18 days after start of menses following treatment courses 1, 2, 3 and 4 respectively. Mean (median) endometrial thickness remained similar to screening at these time points:

- 9.1 (8.0) mm at visit 6.
- 8.3 (8.0) mm at visit 8.
- 8.0 (7.0) mm at visit 9.
- 7.6 (7.0) mm at visit 11.

The percentage of subjects with endometrial thickness > 16 mm was 7.4%, 3.4%, 2.8% and 1.5% respectively. At the post treatment follow up visit, there were 0.9% subjects with endometrial thickness > 16 mm.

Study PGL09-027

The following results related to subjects in the UPA and placebo subgroup. At screening, mean (median) endometrial thickness was 9.9 (9.0) mm, with 4.5% subjects with mean (median) endometrial thickness > 16mm.

Visits 6, B and C occurred 10-18 days after start of menses following treatment courses 1, 2 and 3 respectively. Mean (median) endometrial thickness remained similar to screening at these time points:

- 10.4 (10.0) mm at visit 6; 13.2% subjects with endometrial thickness > 16 mm.

- 9.5 (9.0) mm at visit B; 6.5% subjects with endometrial thickness > 16 mm.

- 8.4 (8.0) mm at visit C; 1.8% subjects with endometrial thickness > 16 mm.

At the post treatment follow up assessment (visit F), mean (median) endometrial thickness was 8.8 (8.0) mm and there were 2.0% subjects with endometrial thickness > 16 mm.

Study PGL07-021

The number of subjects with endometrial thickness > 16 mm varied during the study (assessed by MRI):

- 1 (1.1%) subject in the 5 mg group and 2 (2.0%) subjects in the 10 mg group at screening.

- 10 (10.5%) and 7 (7.1%) in the 5 mg and 10 mg groups respectively at week 13.

- 2 (3.3%) subjects in the 5 mg group and 1 (1.8%) in the 10 mg group at week 38.

The EMA Evaluator noted the median endometrial thicknesses for all treatment groups were slightly lower at week 38 than at screening.

Study PGL07-022

Endometrial thickness was reported to be similar between treatment groups at screening, with approximately 5% of subjects with endometrial thickness > 16 mm. At week 13, 11.3% subjects in the 5 mg group, and 14.6% subjects in the 10 mg had an endometrial thickness > 16mm; for those women not undergoing hysterectomy or endometrial ablation, endometrial thickness > 16 mm was reported for 5.2% and 5.1% subjects in the 5 mg and 10 mg groups respectively at week 17, and 5.5% (5 mg group) and 2.6% (10 mg group) at week 38.

Study PGL09-026

There were 1.5% subjects at screening and 9.1% subjects at week 13 with endometrial thickness > 16mm; the EMA Evaluator notes this is similar to other Phase III studies as discussed above (range 7-15%). At the 3-month post treatment follow up visit for those subjects not undergoing surgical procedure, and not continuing into the extension study PGL09-027 (n=48), there were no subjects with endometrial thickness > 16mm.

> *Evaluator comment: The CHMP requested supplementary information from the Sponsor during the EMA Evaluation process. One question related to final safety results including data for women with endometrial thickness > 16 mm from Part II of Study PGL11-006. The EMA Assessor concluded "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 the study and during the post-treatment follow-up."*

8.3.5.3. *Endometrial biopsies*

The Sponsor states in the short-term and long-term Phase III studies, the endometrial samples were assesses by 3 independent pathologists (blinded to treatment allocation, study visit sequence and each other's assessment).

The pathologist was required to:

- deem specimen adequate or not (only 1 pathologist required to find a specimen adequate for inclusion in analysis).

- make primary diagnosis of either benign endometrium, hyperplasia, or malignant neoplasm (each with sub-classifications).

- observe whether polyps were present or not.

For the primary diagnosis, and observation of polyps, the main diagnosis was the consensus of at least 2 of 3 pathologists; if a different finding was reported by all pathologists, the most severe diagnosis was reported. Note PAEC refers to non-physiological changes (various descriptors).

Study PGL11-006

Endometrial biopsies were taken at screening, and 10-18 days after menses following the end of treatment course 2 (visit 8), treatment course 4 (visit 11) and at 3 months post end of treatment follow up (visit 12). The Sponsor states this is to assess the reversibility of PAEC. Biopsy was taken at visit 9 if the specimen at visit 8 was not considered adequate.

- at screening, 422 (93.8%) biopsies were considered adequate for assessment.
    - all samples were diagnosed as benign endometrium.
    - benign polyps were reported for 7 (1.7%) subjects.
    - non-physiological changes (PAEC) were reported by at least 2 pathologists for 34 (8.1%) biopsies.

- at visit 8, 356 (93.0%) biopsies were considered adequate.
    - there were 3 subjects with hyperplasia:
        - 2 subjects with simple, non-atypical hyperplasia, 1 from each subgroup.
        - 1 subject from the 10 mg group with simple, atypical hyperplasia.
        - the Sponsor states all 3 subjects continued in the study and all returned to benign endometrium without medical or surgical intervention.
    - 1 subject from the 5 mg group had a diagnosis of endometrial adenocarcinoma (considered unrelated to ulipristal and pre-existing).
    - non-physiological changes (PAEC) were reported by at least 2 pathologists for 64 (17.8%) biopsies (29 [16.3%] in the 5 mg group and 35 [19.2%] in the 10 mg group).

- at visit 9, 37 (71.2%) of biopsies were considered adequate.
    - all biopsies were diagnosed as benign endometrium.
    - hyperplastic polyp was reported for 1 subject in the 10 mg group, and benign polyp for 1 subject in the 5 mg group.
    - non-physiological changes (PAEC) were reported by at least 2 pathologists for 7 (18.9%) biopsies.

- at visit 11, 293 (88.5%) of biopsies were considered adequate.

- 1 subject from the 5 mg group had a diagnosis of complex atypical hyperplasia. The Sponsor states at visit 12 this subject had a consensus diagnosis of benign endometrium.

- 1 subject from the 5 mg group had a hyperplastic polyp (different subject from visit 9).

- benign polyps were reported for 4 subjects (1 subject in the 5 mg group and 3 subjects in the 10 mg group).

- non-physiological changes (PAEC) were reported by at least 2 pathologists for 39 (13.3%) biopsies (24 [16.2%] in the 5 mg group and 15 [10.3%] in the 10 mg group).

- at visit 12, 286 (88.3%) biopsies were considered adequate.

   - 1 subject from the 5 mg group had a diagnosis of complex, non-atypical hyperplasia (previous biopsy reported as benign endometrium).

   - 1 subject from the 5 mg group had a diagnosis of benign polyp.

   - non-physiological changes (PAEC) were reported by at least 2 pathologists for 22 (7.7%) biopsies (13 [9.0%] in the 5 mg group and 9 [6.3%] in the 10 mg group).

- there was 1 subject in the 5 mg group with a consensus diagnosis of simple atypical hyperplasia following histology review of material taken at curettage following the SAE of menorrhagia following treatment course 1. A consensus diagnosis of benign endometrium was made at early termination visit 1 month later.

   Evaluator comment: In summary, there were 6 cases of hyperplasia reported. The EMA evaluator stated no endometrial thickening was reported for any of these 6 subjects at the time of hyperplasia diagnosis. Further, the EMA Evaluator commented that there was generally a good agreement between pathologist regarding the presence of hyperplasia, although some disagreement on the level of atypia. See Evaluator comment below.

   Study PGL09-027

- Biopsies were carried out at screening, visit 6 (following treatment course 1 in Study PGL09-026) and at visit E (following treatment course 4; see Table 31 above). Biopsies were only carried out at visit B (following treatment 2) if endometrial thickness was > 18 mm or if there was any clinical reason to do so. Similarly, biopsy was only performed at visit F (post-treatment follow up visit) if there was an abnormal result at visit E.

- The following results were reported for the for the UPA/placebo group continuing into Study PGL09-027 (n=69):

   - at screening, 94.9% had adequate specimen at baseline; all were reported as benign endometrium with nil polyps reported.

   - at visit 6, 94.2% had adequate specimen; all were reported as benign endometrium; 2 subjects (3.1%) had benign polyps.

   - at visit E, 94.0% had an adequate specimen; all were reported as benign endometrium; 1 (2.1%) subject had a benign polyp.

- non-physiological changes were reported by at least 2 pathologists for:

   - 7.1% at screening.

   - 30.8% at visit 6

   - 23.4% at visit E.

- Endometrial biopsy was performed at visit F for subjects with non-physiological change reported by any pathologist at visit E. In the UPA/placebo group, 32 (94.1%) subjects had an adequate specimen at visit F. All were reported as benign endometrium, 2 subjects had a

benign polyp. Non-physiological changes were reported by 2 or 3 pathologists for 16.0% of subjects.

Evaluator comment: The EMA Evaluator noted the total proportion of subjects with non-physiological changes was similar at visit 6 and visit E, i.e., following 1 and 4 courses of treatment (28.7% and 25.3% respectively). For the UPA/ placebo subgroup, the total proportion of subjects with non-physiological changes was slightly less at visit E (23.4%) than visit 6 (30.8%).

Study PGL07-021

- Endometrial biopsies were obtained at screening, week 13 and week 38 for those subjects who did not undergo hysterectomy or endometrial ablation.

- At screening:
    - there were 95.9% biopsies considered adequate.
    - benign endometrium was reported for all except one subject with complex atypical hyperplasia (UPA 5 mg group). This subject was subsequently withdrawn.
    - there were 77.1% (placebo), 71.6% (5 mg group) and 73.5% (10 mg group) subjects who did not have non-physiological changes in the endometrium at screening.
        - non-physiological changes in the endometrium were reported by at least 2 pathologists for n=1 (2.1%) placebo, n=6 (6.3%) and n=1 (1.0%) for placebo, 5 mg and 10 mg groups respectively.
        - there were nil subjects with non-physiological changes in the endometrium reported by all 3 pathologists.

- At week 13:
    - there were 81.3%, 82.1% and 79.6% of subjects with adequate biopsy specimens in the placebo, 5 mg and 10 mg groups respectively.
    - all subjects had benign endometrium; there were no cases of hyperplasia or malignancy reported. - benign polyp was reported for one subject in the 5 mg group and hyperplastic polyp for one subject in the 10 mg group.
    - there were 58.3% (placebo), 12.6% (5 mg) and 15.3% (10 mg group) subjects who did not have non-physiological changes in the endometrium.
        - non-physiological changes in the endometrium were reported by all 3 pathologists for n=0 (0%), n=43 (45.8%) and n=37 (37.8%) for placebo, 5 mg and 10 mg groups respectively.

- At week 38:
    - there were 78.9%, 77.9% and 78.2% of subjects with adequate biopsy specimens in the placebo, 5 mg and 10 mg groups respectively.
    - all except one subjects had benign endometrium; 1 subject in the placebo group had complex atypical hyperplasia reported.
    - benign polyp was reported for one subject in the 5 mg group.
    - there were 68.4% (placebo), 58.4% (5 mg group) and 60.3% (10 mg group) subjects who did not have non-physiological changes in the endometrium.
        - non-physiological changes in the endometrium were reported by all 3 pathologists for n=0 (0%), n=1 (3.1%) and n=3 (3.8%) subjects in the placebo, 5 mg and 10 mg groups respectively.

Study PGL07-022

- Endometrial biopsies were obtained at screening, week 13 and week 38 for those subjects who did not undergo hysterectomy or endometrial ablation.

- At screening:
  – there were 91.8% (5 mg group) and 97.1% (10 mg group) of biopsies considered adequate.
  – benign endometrium was reported for all except 1 subject with simple, non-atypical hyperplasia (UPA 5 mg group).
  – 2 subjects in the 5 mg group had a benign polyp.
  – there were 79.4% (5 mg group) and 82.5% (10 mg group) subjects who did not have non-physiological changes in the endometrium at screening.
    - non-physiological changes in the endometrium were reported by 3 pathologists for n=0 and n=1 (1.0%) for the 5 mg and 10 mg groups respectively.

- At week 13:
  – there were 88.7% and 92.2% of subjects with adequate biopsy specimens in the 5 mg and 10 mg groups respectively.
  – all except 1 subject had benign endometrium; 1 subject in the 5 mg group had simple, non-atypical hyperplasia (different subject compared to screening).
  – benign polyp was reported for 1 subject in the 5 mg group.
  – there were 22.7% (5 mg group) and 20.4% (10 mg group) subjects who did not have non-physiological changes in the endometrium.
    - non-physiological changes in the endometrium were reported by all 3 pathologists for n=38 (39.2%) and n=40 (38.8%) for the 5 mg and 10 mg groups respectively.
    - the EMA Evaluator noted there was wide variation between pathologists regarding histopathological evaluation.

- At week 38 (subset of patients who did not undergo surgery):
  – there were 75.3% and 77.5% of subjects with adequate biopsy specimens in the 5 mg and 10 mg groups respectively.
  – all subjects had benign endometrium; there were no polyps reported.
  – there were 54.5% (5 mg group) and 67.5% (10 mg group) subjects who did not have non-physiological changes in the endometrium.
    - non-physiological changes in the endometrium were reported by all 3 pathologists for n=3 (3.9%) and n=0 subjects in the 5 mg and 10 mg groups respectively.

  Evaluator comment: Studies PGL07-021 and PGL07-022 were the pivotal studies assessed for the original marketing authorisation in the EU (for the 3-month pre-operative indication). The EMA Evaluator stated the following (see EMA Report 1):

  - the rating scale used to assess the endometrial biopsies in the pivotal Phase III studies incorporated description of non-physiological findings that are the result of progesterone receptor modulator treatment; the Evaluator considered the rating scale to assess the biopsies adequate.
  - endometrial data at week 38 in Studies PGL07-021 and PGL07-022 is reassuring regarding findings of concern in the UA treatment groups. The incidence of PAEC at week 38 (6 months post-treatment) was similar to that observed at screening.

- ▪ diverging results of the histopathological endometrial assessment between pathologists underlies the need of PAEC trained pathologists to avoid misdiagnosis in clinical routine (sic).

- ▪ the ongoing Phase III study PGL09-026 and extension PGL09-027 will address long-term effect of prolonged UA treatment on the endometrium, the risk of inappropriate management of endometrial thickening (unnecessary interventions or treatment), the risk of inappropriate diagnosis of endometrial hyperplasia (mistaking PAEC for hyperplasia).

Study PGL09-026

- Endometrial biopsies were taken at:
  - screening
  - visit 6 (after first menstrual bleeding following end of UPA treatment).
  - visit 7b (3 months after end of UPA treatment for those subjects not continuing into the extension study PGL09-027).

- For the UPA/placebo group, there were 94.4%, 93.9% and 90.0% of screening, visit 6 and visit 7b biopsies considered adequate (corresponding values for total population were 95.9%, 93.1% and 95.0%).

- all biopsies were assessed as benign endometrium.

- There were 2 subjects (2.2%) in the UPA/placebo group with benign polyp at visit 6; nil at visit 7b.

- There were no cases of hyperplasia or adenocarcinoma reported.

- non-physiological changes in the endometrium were reported for the UPA/placebo group for 13.1% at screening. 32.5% at visit 6 and 16.7% at visit 7b.

8.3.6. Evaluator comment: discussion of endometrial biopsy results

The CHMP requested supplementary information from the Sponsor during the EMA Evaluation process. Major objection 1 related to endometrial safety. A summary of the questions and EMA Assessor's responses are discussed below.

8.3.6.1. *Clinical aspects: safety*

- *1. Before a conclusion on the endometrial safety of long-term intermittent treatment with ulipristal acetate can be made, further clarifications are needed.*

  a) Further reassurance is needed concerning the importance and long term implications of the 6 cases of hyperplasia documented in the 006 trial. Occurrence of hyperplasia (including atypical hyperplasia), which is claimed normal in this age group of the target population and reversible upon menstruation, should be further discussed and supported by relevant guidance documents and/or expert opinions. This discussion should include aspects related to the proposed mechanism (anovulatory cycles and stable oestradiol levels at mid-follicular phase level).

Key points from the Assessor's comments were:

- The Applicant provided the relevant guidance documents and/or expert opinions regarding differences between endometrial hyperplasia and non-physiological or SPRM Associated Endometrium Changes (PAEC).

Characteristics of endometrial hyperplasia:

- In women with regular ovulations and menstrual periods, the cyclic morphological changes that take place within the uterus cycle have an initial follicular phase during which progestin levels are low.

- After ovulation, the proliferative property of oestrogen on the endometrium is counter-balanced by progesterone….progesterone induces secretory differentiation in the endometrium and is required during each cycle to induce this differentiation and stop the proliferation.

- In an anovulatory cycle, there is excess of oestrogen stimulation and the associated promotion of mitosis is not counter-balanced by progesterone.

- The result is dilated glands lined by a thickened endometrium with frequent mitotic figures. Upon return of ovulation and subsequent progesterone stimulation, the oestrogen stimulation is counter-balanced by progesterone. When progesterone is withdrawn at the end of the luteal phase, the endometrium is shedded, resulting most often in reversibility of the hyperplasia. With increasing age there is a risk of occasional anovulatory cycles in women approaching menopause.

- It is agreed with the Applicant that occasional anovulatory cycles in women approaching menopause often remain without pathological consequences.

- Endometrial hyperplasia is typically the consequence of a prolonged un-opposed oestrogen exposure (Iram, 2010; Lacey, 2012). In premenopausal women, the incidence of hyperplasia is increased by age (Iram, 2010).

Mechanism of action of SPRM/ulipristal:

- SPRMs (including ulipristal acetate) have a different mechanism, resulting in anovulation through a partial inhibition of gonadotropins associated with mid-follicular levels of oestrogen.

- The expert pathologists defined the SPRM's impact on endometrium morphology as non-physiological or PRM Associated Endometrium Changes (PAEC) and concluded that no safety concerns arise from these changes.

- The SPRM-specific changes differ from an unopposed oestrogen effect.

- With the intermittent treatment regimen, and menstruations between each treatment course, the endometrium regularly sheds and renews.

- It is agreed with the Applicant that alteration in endometrial morphology during SPRM/UA treatment clearly differs from characteristics of endometrial hyperplasia.

- Expert statements were provided from the 3 experts; the three experts support the data presented and argumentation made, in particular that ulipristal acetate has a different mechanism of action than unopposed oestrogen effect or PCOS, and that Esmya does not increase the frequency of hyperplasia including when used long term as compared to what is reported in the literature and that the reversibility of hyperplasia cases (even when atypia present) is in line with literature and clinical practice. In addition, the cases of hyperplasia require a simply standardized follow up.

- *b) Updated information regarding the prevalence of endometrial hyperplasia and its spontaneous reversibility during ulipristal acetate clinical trials including complete biopsy set of Study PGL11-006 (Pearl IV)*

It is noted the complete biopsy set of Study PGL11-006 was not available at the time of the EMA evaluation.

Key points from the Assessor's comments were:

- The total number of cases with a diagnosis of endometrial hyperplasia in subjects treated with ulipristal in all Phase III studies combined remains 7 cases.

- Prior to any treatment, a prevalence of endometrial hyperplasia of 1.82% was reported in the target population

    Evaluator comment: the Sponsor stated the following as part of the response - in Study PGL11-006 prior to inclusion, of 555 subjects screened, 493 provided adequate biopsies of which 9 subjects (1.82%) had a diagnosis of endometrial hyperplasia and were therefore not eligible for the study).

- During treatment, there were sporadic cases of endometrial hyperplasia recorded in all treatment groups, independent of the duration of treatment.

- 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.

- The incidence of endometrial hyperplasia was calculated to 0.59% (95% CI: 0.07% to 2.12%) over an 18 months period. 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%.

- The updated tables for hyperplasia/malignant neoplasia overall during ulipristal acetate treatment in clinical trials indicate spontaneous reversibility of hyperplasia.

- *c) Outcome of the 6 cases of endometrial hyperplasia in patients treated with UPA in Study PGL11-006*

Key points from the Assessor's comments were:

- Of these 6 subjects, 5 returned to normal during the course of the study and 3 of them under continued exposure to UPA. A spontaneous resolution of hyperplasia (even with atypia) is previously reported in published literature (Kurman, 1985; Lacey, 2010).

- 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 spontaneously resolved within 3 months following treatment end.

- *d) Comparison of prevalence of endometrial hyperplasia reported in the literature for the target population and incidence/prevalence/frequency of endometrial hyperplasia in ulipristal acetate phase III studies.*

Key points from the Assessor's comments were:

- It is agreed with the Applicant that the population with no gynaecological symptoms 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 25.3% with 0.03% to 1.26% for atypical hyperplasia.

- In ulipristal acetate phase III studies the prevalence and incidence of endometrial hyperplasia rate are below 1% (0.59%, 95% CI 0.07% to 2.12% over an 18 months period) and comparable with the published literature.

- *e) The actual risks of a one-time diagnosis of endometrial hyperplasia*

Key points from the Assessor's comments were:

– Hyperplasia may be asymptomatic but 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 (11y-4.1y).

Key points from the Rapporteur´s overall assessment of Major Objection 1a:

– 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.

– 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.

– One crucial issue to have in mind, is that endometrial hyperplasia in most cases is asymptomatic and therefore may go undetected for quite some time. The discussion by the MAH indicating that this would not be a problem is not entirely supported since atypical hyperplasia may indeed develop to adenocarcinoma and a delay in diagnosis may result in a worsened prognosis. However, the incidence of atypical 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 and does not preclude an approval of repeated, intermittent treatment courses.

- *1. Before a conclusion on the endometrial safety of long-term intermittent treatment with ulipristal acetate can be made, further clarifications are needed.*

- *b) The MAH should discuss how further data can be provided with respect to endometrial safety in the context of long term use of ulipristal in particular considering that endometrial hyperplasia is non-symptomatic and the target population is premenopausal women, often without uterine symptoms. In this context, it should be justified how data from ongoing studies and the planned PASS could provide additional reassurance with respect endometrial safety (OC4 should also be considered as part of the response).*

Key points from the Rapporteur´s overall assessment of Major Objection 1b:

– The Applicant has included the recommendations in the proposed updated version of the SmPC, section 4.4 (see separate SmPC) referring to how to handle patients with abnormal ultrasound findings or abnormal bleedings. These recommendations are supported even though they do not resolve the issue of asymptomatic hyperplasia. However, the incidence of hyperplasia in the phase III studies was low and it is agreed that mandatory endometrial biopsies for all patients with repeated courses of UPA is not indicated.

– The proposed PASS study (PGL14-001) protocol has been adapted and extended to require individual follow–up to 5 years instead of the initially proposed 2 years (see also the assessment of OC4 in the RMP AR). The number of patients is increased from 1200 to 1500, and will only include patients who intend a long-term treatment with UPA.

– In summary, this Evaluator considers the concerns regarding endometrial hyperplasia to have been adequately addressed. It is noted the information in the Precautions section of the proposed PI regarding endometrial changes is consistent with the information in Section 4.4 of the SPC.

8.3.7. Cardiac and vascular disorders

The EMA Evaluator stated there were no signals of increased cardiac risk due to UPA use (during treatment or up to 6 months post-treatment) identified in the short-term Phase III studies PGL07-021, PGL07-022 or PGL09-026. The Sponsor states this was also the case for the long-term studies PGL09-027 and PGL11-006. Further, the EMA Evaluator stated there was no evidence of an increased risk of hypertension, syncope or other cardiac AEs reported.

8.3.8. Hepatobiliary disorders and liver safety

The EMA Evaluator stated there was no evidence of liver toxicity in any of the clinical studies with UPA. Regarding Study PGL11-006, the EMA Evaluator noted a few cases of on-treatment TEAEs related to abnormal liver function, the majority of which were reported during treatment course 1. The Evaluator stated there were no cases of hepatobiliary disorders reported after treatment course 3 and 4.

8.3.9. Nervous System disorders

The Sponsor states headache was one of the most frequent TEAEs reported in the clinical development program of UPA (both for use as emergency contraceptive and treatment of uterine fibroids). Headache was one of the most common TEAEs reported in the short-term Phase III studies (PGL07-021, PGL07-022 and PGL09-026). In the long-term study PGL11-006, headache was reported most frequently during treatment course 1 and lower during subsequent courses. This trend is also noted for Study PGL09-027 (14.4% subjects in treatment course 1 and 3.1-6.5% in subsequent treatment courses). The majority of cases of headache were mild or moderate in intensity in both the short-term and long-term studies.

8.4. Laboratory tests

8.4.1. Liver function

8.4.1.1. Study PGL11-006

It is noted abnormal hepatic function was an exclusion criterion for the study. There was little change in AST, ALT and GGT values throughout the study in either treatment group.

8.4.1.2. Study PGL09-026 and PGL09-027

AST and ALT measurements did not vary greatly during the studies. The EMA Evaluator commented there was no evidence of liver toxicity based on TEAEs for either Study PGL09-026 or PGL09-027.

8.4.1.3. Study PGL07-021

The EMA Evaluator stated the following:

- mildly elevated transaminase levels were reported for approximately 5% subjects in all groups (similar distribution).

- the elevations were generally < 2 x ULN, transient and not associated with changes in other biochemical parameters.

8.4.1.4. Study PGL07-022

The EMA Evaluator stated there "*were no signals of any treatment related changes in liver function tests.*"

8.4.2. Kidney function

There were no abnormalities of any clinical significance noted for kidney function in the short-term or long-term Phase III studies.

8.4.3. Other clinical chemistry

8.4.3.1. Study PGL11-006

Endocrine Parameters

Oestradiol levels were assessed at screening, and end of treatment course 2 and 4. The Sponsor stated there were few on-treatment values outside of the normal range (0 to 399 pg/mL); increased levels considered to be of clinical significance were observed for 4 subjects in the 5 mg group and 1 subject in the 10 mg group at the end of treatment course 4. The Sponsor stated E2 levels generally remained constant during the study, with no overall decrease observed.

Bone mineral density

The EMA Evaluator states the following:

> *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).*

> *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 (PGL09-026/027and 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.*

Lipids

The Sponsor states the number of subjects with total cholesterol > ULN was 41.4% at screening, and at visit 12 was 52.7%. The Sponsor states the ratio of total cholesterol/HDL did not change during the study.

There were no changes in lipids or coagulation parameters considered to be of clinical significance.

8.4.3.2. Studies PGL09-026 and PGL09-027

There were no identifiable trends in the summary data for endocrine measurements (E2, ACTH, TSH and prolactin) reported in either study. During the PGL09-026 and PGL09-027 studies the mean cholesterol levels varied, with no identifiable pattern observed.

8.4.3.3. Study PGL07-021

Endocrine parameters are discussed in detail by EMA Evaluator. The key findings were:

- E2 values with ulipristal treatment correspond to mid-follicular levels for pre-menopausal women.

- the mean progesterone values in the ulipristal group were lower than those in the placebo group at week 13 indicating anovulation in a majority of patients. Maximal values > 5.0 mg/mL indicate a persistence of ovulation in a minority of women treated with ulipristal.

- there was little change in median ACTH levels throughout the treatment period, with no evidence of difference between the ulipristal groups and placebo.

- there was some variation in prolactin levels in the three groups during the treatment period, with no obvious finding with regard to ulipristal treatment.

- there was some evidence of a difference in FSH between ulipristal and placebo at week 13 (levels lower in the ulipristal groups compared with placebo.

The EMA Evaluator stated increases in mean cholesterol LDL cholesterol and triglycerides from baseline to end of study were evident in all treatment groups, with increased from baseline in mean cholesterol and LDL cholesterol higher for the ulipristal groups compared with placebo.

8.4.3.4.   Study PGL07-022

Endocrine parameters are discussed in detail by EMA Evaluator in the EMA Report 1. The key findings were:

- mean and median P4 (progesterone) values were very low in all treatment groups suggesting absence of ovulation in most subjects.

- ACTH values were similar across treatment groups.

- no evidence of difference in TSH values in treatment groups.

- mean and median prolactin values remained unchanged in the UPA groups during treatment.

- median FSH levels were lower at week 13 than at baseline for all groups.

- median E2 levels were higher in the ulipristal groups than the GnRH group. Within a few weeks of discontinuation, E2 levels had increased.

The EMA Evaluator stated ulipristal was associated with a slight rise in mean total cholesterol and mean LDL cholesterol during treatment.

> *Evaluator comment: The EMA Evaluator noted the following regarding endocrine parameters:*
>
> *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 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.*

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.

8.4.4. Haematology

It is of note haemoglobin values were not provided in SI units for any of the Phase III studies discussed below.

8.4.4.1. Study PGL11-006

The mean (median) haemoglobin value at screening was 12.27 (12.50) g/dL (Safety set; normal range 11.5 - 15.5 g/dL). At visit 12 (end-of-study follow up visit), mean (median) haemoglobin was 12.90 (13.10) g/dL. The number of subjects with haemoglobin levels within the normal range increased during the study; 164 (72.9%) subjects from the 5 mg group and 162 (75.0%) subjects from the 10 mg group at the start of treatment course 1, to 152 (89.9%) and 159 (94.6%) subjects from the 5 mg and 10 mg groups respectively at the end of treatment course 4.

Similarly, improvements were observed for haematocrit values from baseline (mean [median] 0.40 [0.40]) to the end of treatment course 4 (mean [median 0.42 [0.42]).

8.4.4.2. Study PGL09-027

Mean (median) values for haemoglobin and haematocrit at screening were 12.42 (12.90) and haematocrit 0.39 (0.40) respectively. Values for both haemoglobin and haematocrit remained higher than screening levels throughout the study.

8.4.4.3. Study PGL07-021

It is noted anaemia (defined as haemoglobin ≤10.2 g/dL) was an inclusion criterion for this study, and all subjects received concomitant oral iron therapy during the treatment period. At end of study treatment, 81 (85.3%) subjects from the 5 mg and 84 (89.4%) subjects from the 10 mg groups had haemoglobin values >12g/dL (vs. with 37 (77.1%) subjects of the placebo group). Increases in haematocrit from baseline were also observed in all treatment groups, with statistically significantly higher increases in both the UPA groups compared to placebo.

8.4.4.4. Study PGL07-022

At the end of treatment, mean haemoglobin and haematocrit had increased from baseline in both ulipristal groups. The EMA Evaluator noted the overall percentage of subjects with haemoglobin > 12 g/dl and haematocrit > 36% increased during the study.

8.4.4.5. Study PGL09-026

The mean (median) haemoglobin value at screening was 12.51 (12.90) g/dL. At the end of ulipristal treatment, the mean (median) haemoglobin value had risen to 13.26 (13.60) g/dL. Similarly, mean (median) haematocrit levels were higher at the end of treatment (0.41 [0.42]) compared to screening (0.39 [0.40]).

8.4.5. Electrocardiograph

There were no clinically significant ECG abnormalities reported in the Phase III studies.

8.4.6. Vital signs

There was no evidence treatment with ulipristal had any effect on blood pressure or pulse rate during the Phase III studies (not monitored in Phase II studies).

8.4.7. Other safety issues

The CHMP requested supplementary information from the Sponsor during the EMA Evaluation process. The potential risk of breast cancer was addressed under 'Other Concerns' as discussed below.

- *The MAH should discuss 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 estradiol levels.*

Key points from the Assessor's comments were:

- It is agreed that the non-clinical, clinical and post-marketing data do not indicate an increased risk for breast cancer with ulipristal acetate long-term treatment. In the reviewed literature, SPRMs are supposed to play rather a protective role on breast tissue and are considered as putative hormonal agents for the treatment of breast cancer (Benagiano, 2008). Issue resolved.

8.5. Post-marketing experience

There were 5 PSUR documents provided, and progress report for the post-authorisation safety study PGL10-014. Key findings of the PSURs are discussed below. In summary, there were no new safety issues identified and no regulatory action taken for safety reasons.

- PSUR number 5 covers the period 23rd February 2014 to 22nd August 2014.
  - interval marketing exposure was estimated at approximately 47,300 patients.
  - cumulative marketing exposure was estimated at around 107,500 patients.
  - there were no cases of liver toxicity in clinical trials; there was 1 report from a spontaneous source, but not qualifying as drug induced liver injury.
  - no cases 'inappropriate management of endometrium thickening' or 'inappropriate diagnosis of endometrial hyperplasia' was received from clinical trials and other sources were not conclusive.
- PSUR number 4 covers the period 23rd August 2013 to 22nd February 2014.
  - interval marketing exposure was estimated at around 32,700 patients.
  - cumulative marketing exposure was estimated at around 60, 500 patients
  - there were no safety issues identified.
- PSUR number 3 covers the period 23rd February 2013 to 22nd August 2013.
  - interval marketing exposure was estimated at approximately 14,500 patients.
  - cumulative marketing exposure was estimated at around 27,800 patients.
  - there was 1 case each of 'inappropriate management of endometrium thickening' and 'inappropriate diagnosis of endometrial hyperplasia'. The Sponsor states the educational programme (Physician's Guide to Prescribing and Pathologists brochure) was implemented in countries where Esmya is marketed).
  - two cases of potential liver toxicity were received; neither confirmed the important potential risk of 'drug induced liver injury'.
- PSUR number 2 covers the period 23rd August 2012 to 22nd February 2013.
  - interval marketing exposure was estimated at approximately 8,500 patients.
  - cumulative marketing exposure was estimated at approximately 12,900 patients.

- – there was 1 case of 'inappropriate management of endometrium thickening'.
- PSUR number 1 covers the period 23rd February 2012 to 22nd August 2012.
  - – 5,500 patients were exposed to Esmya during the review period.
  - – There were no new relevant safety findings identified.

Study PGL10-014 is a multi-centre, prospective, non-interventional study of women treated with UPA 5 mg as pre-operative treatment of moderate to severe symptoms of uterine fibroids . There are 1568 patients enrolled; patients will be followed up during treatment and for up to 12 months following treatment discontinuation, for a total of up to 15 months follow up. In the second yearly progress report (dated 9th May 2014, covering the period 24th May 2012 - 15th April 2014) the Sponsor stated 1546 patients enrolled at the cut-off, with 936 patients have had at least one post-baseline visit; there have been no safety concerns identified at the time of the report.

8.6.   Evaluator's overall conclusions on clinical safety

The safety profile for UPA has been well described in the data provided. Overall UPA is generally well tolerated; the most common adverse events were headache and hot flush, most of which were mild or moderate in intensity. Further, in the long-term studies, adverse events were more common during the first treatment course than in subsequent treatment courses.

The main safety issue identified related to endometrial safety. Concerns raised by the CHMP during the EMA evaluation process are considered to have been adequately addressed by the EMA Assessor in the response to further information sought by the CHMP. The EMA Evaluator concluded:

> 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.

This Evaluator endorses these comments. There have been no additional safety concerns identified in the available post-marketing data.

9.   First round benefit-risk assessment

9.1.   First round assessment of benefits

The benefits of ulipristal in the proposed usage are:

- There is a lack of available long-term medical treatment options in Australia for women with symptomatic uterine fibroids.
- Clinically relevant improvement in bleeding profile as well as reductions in myoma volume, uterine volume and improvement in quality of life parameters have been demonstrated with up to 4 repeated intermittent courses of ulipristal acetate.

9.2.   First round assessment of risks

The risks of ulipristal in the proposed usage are:

- Endometrial safety - potential identified risks include changes in endometrial thickness, and endometrial hyperplasia. Concerns regarding these issues have been addressed during the EMA Evaluation. The EMA Evaluator noted frequency of endometrial hyperplasia was low in the pivotal study and there were fewer subjects with endometrial thickness > 16 mm with successive treatment courses. Further, the frequency of PAEC did not increase with repeated treatment courses, and rapid reversibility of these changes was observed following treatment completion and subsequent menstruation.

- There are no long-term follow-up data following repeated intermittent course of ulipristal acetate to ascertain the sustainability of treatment effect, and long-term safety issues.

9.3. First round assessment of benefit-risk balance

The benefit-risk balance of ulipristal acetate 5 mg, given the proposed usage, is uncertain at this point in time. The benefit-risk balance will be discussed at Round 2.

10. First round recommendation regarding authorisation

Recommendation regarding authorisation will be made at Round 2.

11. Clinical questions

- 1. The proposed PI contains the following information regarding endometrial changes in the Precautions section:

  – Reversible increase in thickness of the endometrium may occur under treatment. If the endometrial thickening persists after return of menstruations during off-treatment periods or beyond 3 months following the end of treatment courses, it may need to be investigated as per usual clinical practice to exclude other underlying conditions.

  – 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. In case of persistent thickening of the endometrium and/or an altered bleeding such as inter-menstrual bleeding, investigation including endometrial biopsy should be performed in order to exclude other underlying conditions.

  – In case of hyperplasia (without atypia), monitoring as per usual clinical practice (e.g. a follow-up control 3 months later) would be recommended. In case of atypical hyperplasia, investigation and management as per usual clinical practice should be performed.

  Given the recognised potential endometrial changes associated with ulipristal use, please discuss the proposed prescriber educational program to ensure target prescribers are aware of the need for periodic monitoring and appropriate follow up of women using ulipristal for the management of uterine fibroids.

- 2. Are there long-term follow up efficacy and safety data for the 457 patients exposed to ulipristal acetate 5 mg or 10 mg for four 3 month courses (including bleeding profile, myoma size, endometrial safety)? Are there data available regarding the number of subjects who have undergone a surgical procedure?

- 3. The GnRH agonist leuprorelin is not registered in Australia for use in the management of uterine fibroids, although goserelin 3.6 mg is registered for this indication. The Clinical Expert stated in the Clinical Overview "the two GnRH agonists being similar, the active

comparator selected in the study PGL07-022 and study findings are thus appropriate to conclude about the benefit of Esmya over medical therapies currently registered in Australia to manage uterine fibroids".

Please provide further information to justify the statement "the two GnRH agonists being similar".

- 4. Given Study PGL-W-001 was not considered conclusive regarding use in moderate hepatic impairment, are further studies planned to assess the use of ulipristal acetate in women with hepatic impairment?

- 5. Regarding Study PGL11-006, please provide regarding the frequency of treatment related adverse events related to excessive uterine bleeding for subjects in Study PGL11-006 during and after ulipristal acetate treatment course 3 and treatment course 4.

12. Second round evaluation of clinical data

12.1. Question 1

- 1. The proposed PI contains the following information regarding endometrial changes in the Precautions section:

  – Reversible increase in thickness of the endometrium may occur under treatment. If the endometrial thickening persists after return of menstruations during off-treatment periods or beyond 3 months following the end of treatment courses, it may need to be investigated as per usual clinical practice to exclude other underlying conditions.

  – 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. In case of persistent thickening of the endometrium and/or an altered bleeding such as inter-menstrual bleeding, investigation including endometrial biopsy should be performed in order to exclude other underlying conditions.

  – In case of hyperplasia (without atypia), monitoring as per usual clinical practice (e.g. a follow-up control 3 months later) would be recommended. In case of atypical hyperplasia, investigation and management as per usual clinical practice should be performed.

    Given the recognised potential endometrial changes associated with ulipristal use, please discuss the proposed prescriber educational program to ensure target prescribers are aware of the need for periodic monitoring and appropriate follow up of women using ulipristal for the management of uterine fibroids.

12.1.1. Sponsor's response

One major target tissue for SPRM action is the endometrium where they exert specific effects, some of which are new and unfamiliar to pathologists and gynaecologists. This spectrum of novel histological changes are now well characterised as "PRM associated endometrial changes-PAEC": These changes have not been observed with other agents and the resulting endometrial morphology may be new and unfamiliar to pathologists. It is important that both clinicians and pathologists are aware of these changes, and that they know how these changes are differentiated from the proliferative endometrial response to unopposed oestrogen and forms of endometrial hyperplasia. Appropriate awareness would mitigate the risk for them to inappropriately mistaken PAECs for pathological entities such as simple endometrial hyperplasia.

Other than the detailed information provided in the Product Information (PI) for adequate monitoring of endometrial changes under intermittent treatment with ulipristal 5 mg daily, two documents are included in the proposed Risk Management Plan to guide health care providers and pathologists in their understanding and management of those effects. The latest versions submitted in EU are provided in the S31 response package in appendix of the Risk Management Plan.

The first document is aimed to prescriber physicians, and is intended to describe these changes and to propose a schedule for the management of endometrial thickening in clinical practice. The document includes key information about the therapeutic indication, and the posology of ulipristal 5 mg intermittent treatment for fibroid symptoms. It describes the occurrence of endometrial thickening and specific histological changes (PAECs) while also providing important recommendations for management schedule. The document also provides the well-established criteria for differentiation between PAECs, hyperplasia and endometrial adenocarcinoma.

This 6 pages long document will be used in a similar way as in Europe for the Australian physicians after discussions with prominent field specialist experts at the time of launch in Australia. The main purpose of this document is to increase gynaecologists awareness of the endometrial thickening under treatment and provide them with clear management guidance to avoid unnecessary interventions and hospitalisations. The document also explains the occurrence of PAECs to prescribers, in order to optimize their requests to pathologists when a biopsy sample is sent to a pathologist for analysis (mentioning of the current treatment and specific elements to look for).

The second document is a guide aimed to pathologists, and is intended to describe these changes and to facilitate appropriate histopathologic endometrial assessment in pathology practice. The document was prepared by Dr Alistair Williams, one of the three pathologists in charge of the centralized reading of the phase III trials endometrial pathology slides. The guide describes

- the specific findings in the morphology of endometrium (PAECs) as reported in the two large short term Phase III randomized double-blind controlled clinical trials (PGL07-021/PEARL I and PGL07-022/PEARL II) where patients with symptomatic uterine fibroids were treated with 5 mg or 10 mg of ulipristal acetate once daily for 3 months.

- a summary of the differences in histological features of PAEC, unopposed oestrogen effect, and endometrial hyperplasia

- representative images from PAECs, unopposed oestrogen effect, and endometrial hyperplasia (a CD-ROM storing the representatives images with high resolution is also provided as an aid)

This 16-page document will be used in a similar way as in Europe for the Australian pathologists after discussions with specialist experts at the time of launch in Australia. One major target tissue for SPRM action is the endometrium where they exert specific effects, some of which are new and unfamiliar to pathologists and gynaecologists. This spectrum of novel histological changes are now well characterised as "PRM associated endometrial changes-PAEC": These changes have not been observed with other agents and the resulting endometrial morphology may be new and unfamiliar to pathologists. It is important that pathologists are aware of these changes, and that they know how these changes are differentiated from the proliferative endometrial response to unopposed oestrogen and forms of endometrial hyperplasia. Appropriate awareness would mitigate the risk for them to inappropriately mistaken PAECs for pathological entities such as simple endometrial hyperplasia. The main purpose of this exhaustive document is to improve assessment of PAECs and enable correct differential diagnosis of the endometrial effects of PRMs from other variations or changes in the

endometrium including unopposed estrogen effects or various forms of endometrial hyperplasia by pathologists.

This specialised educational material for pathologists enhances understanding of the "class effect" of SPRMs on endometrial histology and improve the assessment of the endometrial effects of SPRMs.

In 2015, a survey was conducted in 20 European countries where the educational program materials had been distributed to HCPs (gynaecologists and pathologists) to measure effectiveness of the proposed education materials for Esmya® (see PREPAR report in Module 5.3.6). The results of the surveys documented the abovementioned HCPs' awareness and understanding around the following key messages of the Educational Program:

For the gynaecologists:

- Appropriate knowledge about the occurrence and appropriate management of endometrium thickening in patients treated with Esmya® including the need to inform the pathologist that the patient was treated with Esmya® if biopsies/surgical samples are sent for histological analysis;

- The limitation to three months total treatment course duration.

For the pathologists:

- Awareness of PAEC, including its main features and appropriate histological diagnosis of PAEC, which should not be mistaken for unopposed oestrogen effect and endometrial hyperplasia.

The overall proportion of contacted gynaecologists who answered to the survey was 4.75%.

However, the results were different between the different countries and in the following countries, the proportion was higher than 5%: Czech Republic, Estonia, Hungary, Latvia, Lithuania, Poland, Portugal, Romania and Slovakia.

It was observed that the majority of the gynaecologists (n=1324, 50.09%) had previous experience prescribing Esmya. Conversely, the vast majority of the pathologists (n=95, 82.61%) did not have previous experience working with or knowledge of SPRMs or Esmya®. The total number of gynaecologists passing the survey was 2171 (82.1% of the respondents). For the pathologists, the overall proportion of these HCPs who answered to the survey was 1.91% but in seven countries it was equal or higher than 5%: Czech Republic, Estonia, Latvia, Lithuania, Portugal, Romania, and Slovenia. The mean total score among the pathologists was 79.0% (SD 17.2) and 89 pathologists (77.4% of the respondents) passed the survey.

The results of this survey conducted in Europe demonstrate the effectiveness of the educational material, as 82% of the gynaecologists and 77% of the pathologists passed the survey. The questions HCPs answered incorrectly could have been subject to interpretation, especially by pathologists.

In total, more than 90% of the gynaecologists and more than 87% of the pathologists considered the material useful in providing the relevant information on the use of Esmya® and its associated safety and endometrium changes.

The Applicant believes that, together with a detailed PI containing clear management guidelines and educational information about the endometrial changes associated to the intermittent use of ulipristal 5 mg, these comprehensive educational documents will ensure adequate awareness among physicians and pathologists managing patients treated with ulipristal treatment for symptomatic fibroids. The European experience since the first launches of Esmya has allowed many improvements to these 2 documents and to the PI guidelines for management of the endometrial effect. This acquired experience should allow an adequate awareness, and thus appropriate managements of endometrial changes in Australia.

12.1.2. Evaluator comment

The education materials comprise of a document aimed at prescriber physicians, and a separate document intended for pathologists. The Esmya: Physicians' Guide to Prescribing program provides information and guidance with respect to endometrial histological changes and endometrial thickness. Regarding this document, the Sponsor states: "*The main purpose of this document is to increase gynaecologists awareness of the endometrial thickening under treatment and provide them with clear management guidance to avoid unnecessary interventions and hospitalisations. The document also explains the occurrence of PAECs to prescribers, in order to optimize their requests to pathologists when a biopsy sample is sent to a pathologist for analysis*".

Essentially the physician prescribing guide document is targeted to gynaecologists. As part of the Round 2 response, the Sponsor is asked to comment on the use of Esmya by other clinicians, such as general practitioners.

The Evaluator notes the Sponsor conducted a survey of gynaecologists and pathologists regarding the effectiveness of the education materials, however, the response rate was generally low (4.75% for gynaecologists and 1.91% for pathologists). Expert clinical advice regarding adequacy of the proposed education program is recommended.

12.2. Question 2

- 2. Are there long-term follow up efficacy and safety data for the 457 patients exposed to ulipristal acetate 5 mg or 10 mg for four 3 month courses (including bleeding profile, myoma size, endometrial safety)? Are there data available regarding the number of subjects who have undergone a surgical procedure?

12.2.1. Sponsor's response

Four 3-month courses of ulipristal acetate and the associated drug free interval and follow-up period correspond to study duration of about 21 months (i.e. patients enrolled in PGL09-027 (Pearl III extension) and PGL11-006 (Pearl IV) studies have been followed for close to 2 years) and eight 3-month courses of ulipristal acetate and the associated drug free interval and follow-up period correspond to study duration of about 42 months (i.e. patients enrolled in PGL11-024 have been followed for close to 4 years). No long term follow-up information is currently available for patients who completed the 4 courses of treatment in study PGL11-006.

Study PGL11-024 (extension of PGL09-027 itself the extension of PGL09-026) assessed the efficacy and safety of ulipristal acetate 10 mg for 4 additional treatment courses i.e. over a total of 8 intermittent 3-month treatment courses. Long term follow-up information is available for 64 subjects who completed Pearl III extension 1 (PGL09-027) and opted to continue into the second open label extension of the study (PGL11-024).

Of the 99 subjects who completed PGL09-026 and PGL09-027 studies, 64 subjects opted to continue in to the second extension study (PGL11-024). A total of 64 (100.0%), 62 (96.9%), 56 (87.5%) and 54 (84.4%) subjects started ulipristal treatment courses 5, 6, 7 and 8, respectively. All subjects enrolled into the study received open-label treatment with 10 mg tablets, administered orally once daily. In this extension (PGL11-024), Norethisterone acetate (NETA) treatment was not continued, as a 10-day course of NETA treatment following ulipristal was not shown to add significant benefit. This study included 4 treatment courses. Each treatment course consisted of 3-months (84 days) once daily oral treatment with 10 mg. Treatment courses were separated by a drug-free period, until the start of second menses following the end of the previous treatment course.

12.2.1.1. Myoma volume reduction

The decrease in total volume of the 3 largest myomas observed during study PGL09-027 (first 4 courses of treatment) was maintained in most subjects after a mean [median] gap between the

follow-up visit F of PGL09-027 and visit I of PGL11-024 was 103.9 [91.0] days). During PGL11-024 the reduction in total myoma volume was maintained for most of the subjects up to the 3 month follow-up visit. The mean (median) reduction from screening during studies PGL09-026, PGL09-027 and PGL11-024 are shown in Table 13.

Table 13. Percentage of change in mean and median myoma volume from screening in studies PGL09-026, PGL09-027 and PGL11-024.

	PGL09-026 end of course 1	PGL09-027 After menses (following course 4)	PGL09-027 At follow-up (3 months after treatment end)	PGL11-024 After course 6	PGL11-024 After course 8	PGL11-024 At follow up (3 months after treatment end)
% change from screening mean (median)	-53.83% (-59.19%)	-56.55% (-77.30%)	-33.63% (-63.91%)	-1.06% (-68.87%)	-28.46% (-67.10%)	-15.16% (-70.34%)

The mean (median) total volume of the three largest myomas at screening was 68.13 cm^3 (41.39 cm^3). In study PGL09-026), the mean (median) percent change from screening was -53.83% (-59.19%). The median reduction was maintained 10-18 days after the first menstruation following treatment course 1 in study PGL09-026 and further decreased after the first menstruation following treatment courses 2, 3 and 4 in study PGL09-027 where the largest reduction was seen after treatment course 4, with a mean (median) percent change from screening of -56.55% (-77.30%).

In study PGL11-024, the mean (median) reduction from screening at the beginning of the study was -33.63% (-63.91%). Overall, for all subjects 10-18 days after the first menstruation following treatment courses 6 and 8 and follow-up visit, the mean (median) percent change from screening was -1.06% (-68.87%), -28.46% (-67.10%) and -15.16% (-70.34%), respectively. The distribution between mean and median results were due to skewed distributions, with a few outlying subjects having a larger influence on the mean values than the medians.

In terms of the percentage of subjects with ≥25% and ≥50% reduction in the total volume of the 3 largest myomas identified at screening, at the beginning of study PGL11-024, 46 (73.0%) subjects had a volume reduction of ≥25% and 39 (61.9%) subjects had a volume reduction from screening of ≥50%. The percentages did not change much for the remainder of the study. At 3 month follow-up, 39 (76.5%) subjects had a volume reduction from screening of ≥25% and 34 (66.7%) subjects had a volume reduction of ≥50%.

12.2.1.2. Uterine bleeding characteristics

Treatment courses of 10 mg/day of ulipristal acetate demonstrate repeatedly and consistently a very efficient bleeding control under treatment, with a clear benefit demonstrated (with all efficacy endpoints met) when treatment is given up to 4 courses of 3-month each. The benefit under treatment is maintained during off-drug intervals. A progressive reduction of menstrual bleedings with repeated courses was observed.

The first menses post-screening in study PGL09-026, days 1 to 8, had a mean (median) PBAC score of 284.1 (205.5). There was a reduction, on average, for the 8 day PBAC score for the first menstruation post-treatment courses 1, 2, 3 and 4, with a mean (median) PBAC score of 131.6 (89.0), 85.5 (48.5), 79.9 (36.0) and 65.4 (31.0), respectively. The mean (median) PBAC score of the first menstruation at re-start of treatment in PGL11-024 had increased compared to those post-treatment courses 1, 2, 3 and 4, with a mean (median) of 148.0 (84.0). However, this was

still lower than the PBAC score for the first menses post-screening, with a mean (median) change of -129.9 (-88.5).

In study PGL11-024, myoma symptom control was assessed with a Global Study Treatment Satisfaction Questionnaire (GSTSQ). Subjects completed the GSTSQ at every visit: visit I (approximately 3 months after treatment course 4), visit II (10-18 days after the first menstruation following treatment course 6), visit III (10-18 days after the first menstruation following treatment course 8) and visit IV (3 month follow-up after last dose of treatment course 8). Two questions are specifically related to bleeding:

- For the control of uterine bleeding question 2: How satisfied or dissatisfied are you with the way the study drug relieves the uterine bleeding due to your fibroids symptoms? Question 4: How do you estimate your menstrual bleeding now compared to before the very first intake of this study drug? For the control of uterine bleeding question 2, the percentage of subjects who reported being either very satisfied or extremely satisfied were 76.6% at initial visit, 78.3% at visit II, 83.6% at visit III and 76.5% at visit IV. Only one subject at visit I reported being dissatisfied and no subjects reported being very dissatisfied or extremely dissatisfied.

- For the question evaluating menstrual bleeding compared to before first intake of study drug (before starting study PGL09-026, PEARL III) (Question 4), responses ranged from 1=much less heavy to 5=much heavier. The percentage of subjects who reported either much less heavy or a little less heavy were 79.7% at visit I, 93.3% at visit II, 95.9% at visit III and 92.2% at visit IV. Two subjects reported bleeding being a little heavier at visit IV, and one subject reported bleeding being much heavier at visit I.

In summary, the majority of subjects (>75%) were either very or extremely satisfied with control of uterine bleeding throughout the study, and menstrual bleeding compared to before the first intake of ulipristal was less heavy (either much less or a little less heavy) in almost 80% of subjects at the start of PGL11-024 and increased to almost 96% of subjects at visit III (10 18 days after first menstruation following treatment course 8). Between 60-80% of all subjects reported being either very or extremely satisfied with the control of fibroid symptoms and overall satisfaction questions at all visits including visit IV (3 month follow-up), demonstrating sustained improvement of symptoms.

12.2.1.3. *Surgery*

In Study PGL09-026, subjects could choose after the first treatment course to undergo surgery, drop out or continue in the extension Study PGL09-027. From initially 209 subjects recruited, 27 (12.9%) subjects underwent surgery at the end of Study PGL09-026 and 132 (63.2%) subjects chose to continue in the extension study. Following all 4 treatment courses, a total of 107 subjects did not have surgery performed during or prior to the end of the treatment course 4.

During PGL11-024, surgery was performed on 4 out of 64 (6.3%) subjects; for 3 of these, surgery was not initially planned at the start of PGL09-026. Of the 4 subjects that had surgery performed, 2 had a laparotomic hysterectomy, 1 had an abdominal hysterectomy and 1 had surgery but the procedure was 'not known' (the subject had planned to undergo laparoscopic myomectomy). The decision drivers for the 4 subjects that had surgery performed were reported as 'mainly driven by subject request' for 3 subjects and 'equal influence' for 1 subject (whose surgery was unplanned). Three subjects reported the main reason for surgery as 'insufficient efficacy of treatment', and for one subject no reason was provided except the comment 'abdominal hysterectomy'.

Overall, in all Phase III studies, including long term studies, only very few subjects discontinued treatment in order to undergo surgery which demonstrates a good compliance and good patient satisfaction to treatment.

12.2.1.4. Treatment emergent adverse events

There have been no deaths during studies PGL09-026, PGL09-027 or PGL11-024. Treatment emergent adverse events were reported as either on- or off-treatment, depending on timing in relation to each ulipristal treatment course. No SAEs were reported during PGL11-024.

On treatment emergent AEs in course 1 (study PGL09-026) and courses 5 to 8 (Study PGL11-024) are summarized in Table 14.

Table 14. General Summary of On-Treatment Emergent Adverse Events Presented by Treatment Course (PGL11-024, Full Analysis Set).

	Treatment Course 1			Treatment Course 5			Treatment Course 6			Treatment Course 7			Treatment Course 8		
	n	N	%	n	N	%	n	N	%	n	N	%	n	N	%
Number of subjects receiving ulipristal acetate		64			64			62			56			54	
On-treatment TEAE	68	32	50.0	14	10	15.6	15	12	19.4	11	8	14.3	6	5	9.3
Severe On-treatment TEAE	1	1	1.6	0	0	0.0	1	1	1.6	0	0	0.0	0	0	0.0
Ulipristal acetate related On-treatment TEAE	24	13	20.3	1	1	1.6	1	1	1.6	3	3	5.4	0	0	0.0
Serious On-treatment TEAE	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
Serious ulipristal acetate Related On-treatment TEAE	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
On-treatment TEAE With Action Taken with ulipristal acetate was "Drug Withdrawn"	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
On-treatment TEAE Leading to Study Withdrawal	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0

n = No. of Events, N = No. of Subjects with Event, % = 100*(No. of Subjects with Event/No. of Subjects receiving ulipristal acetate for each treatment course).

TEAE: Treatment emergent adverse events are defined as events whose start date is on or after the first dose of study drug.

On-treatment TEAE: defined as events whose start date is on or after the first dose of ulipristal acetate within each treatment course up to and including 7 days after the last dose of ulipristal acetate. For treatment course 1 to 4, this included up to 7 days of double-blind treatment (placebo/NETA) that was planned to be administered for 10 days following the end of each course of ulipristal acetate.

Overall, during treatment courses 1-8 of the study, 47 (73.4%) subjects reported 189 on-treatment TEAEs. The incidence of on-treatment TEAEs reported was highest during treatment course 1, 68 events reported by 32 (50%) subjects, decreasing to 15 (23.4%) subjects reporting 17 and 27 TEAEs during treatment courses 2 and 3, respectively. Following treatment courses 1-8 of the study, 43 (67.2%) subjects reported 107 off-treatment TEAEs. No trends were observed in frequency or type of TEAEs with repetition of treatment courses.

One subject was diagnosed as pregnant during treatment course 5, with an outcome of ectopic kidney in the child. One subject withdrew from PGL11-024 approximately 2 months following the end of treatment course 7, as she chose to undergo an abdominal hysterectomy. One AESI of "endometrial thickening" (PT: endometrial hypertrophy) of mild intensity was reported during treatment course 7; the TEAE was considered related to ulipristal and was resolved 6 weeks later.

During treatment courses 1-8, the majority (98.4%) of all on-treatment TEAEs were rated as being of mild or moderate intensity; of the 3 TEAEs of severe intensity only one occurred during PGL11-024, a report of bronchitis during treatment course 6, which was considered unrelated to ulipristal. Following treatment courses 1-8, the majority (95.3%) of all off-treatment TEAEs were rated as being of mild or moderate intensity; of the 5 TEAEs of severe intensity only one occurred during PGL11-024, a report of sciatica following treatment course 8, which was considered unrelated to ulipristal.

During treatment courses 1-8, the most commonly reported on-treatment TEAE was headache, with the greatest incidence during treatment course 1: headache was reported by 7 (10.9%) subjects during treatment course 1, none during treatment course 2, by 3 (4.7%) subjects

during treatment course 3, by 2 (3.1%) subjects during treatment courses 4 and 5, then by 3 (4.8%), 2 (3.6%) and 2 (3.7%) subjects during treatment courses 6, 7 and 8, respectively. Overall, following treatment courses 1-8, the most commonly reported off-treatment TEAE was dysmenorrhoea, in 5 (7.8%) subjects.

A total of 20 (31.3%) subjects experienced at least one on-treatment TEAE considered to be ulipristal-related. The frequency of treatment related TEAEs occurring under treatment did not increase under repeated treatment courses in Study PGL11-024 (20.3%, 3.1%, 10.9%, 3.1%, 1.6%, 1.6%, 5.4%, 0% in treatment courses 1,2,3,4,5,6,7 and 8 respectively).

Following treatment courses 1-8, a total of 8 (12.5%) subjects experienced 9 off-treatment TEAEs considered to be ulipristal-related. Following treatment courses 1-8 of the study, 43 (67.2%) subjects reported 107 off-treatment TEAEs. The most commonly reported off-treatment TEAE was dysmenorrhoea, in 5 (7.8%) subjects and a total of 8 (12.5%) subjects experienced 9 off-treatment TEAEs considered to be related, including hot flush (2 subjects). No trends were observed in frequency or type of TEAEs with repetition of treatment courses.

Overall, there was no evidence that any specific TEAE increased in frequency or intensity as the number of ulipristal treatment courses increased, nor were any unexpected TEAEs reported during PGL11-024.

12.2.1.5. Endometrial safety

It was shown that repetition of treatment courses with ulipristal acetate did not increase the occurrence / frequency of endometrial findings of concern, i.e. hyperplasia or adenocarcinoma, no cases were reported during study PGL11-024.

No additional observations were reported for biopsy samples during study PGL11-024 except the presence of polyps, seen for 2 subjects at visit I and 2 subjects at visit III. At visit I, hyperplasic polyp was diagnosed for one subject and benign polyp for one subject; for both of these a visit II biopsy was not done, but the polyps were absent at the visit III biopsy. At visit III, benign polyp was diagnosed for 2 subjects (absent at visit IV biopsy).

Endometrium thickness

The median endometrium thickness during PGL11-024 remained below that seen at screening, with no evidence of an increase in the number of subjects with a thickness >16 mm as the number of ulipristal treatment courses increased. At screening (PGL09-026), for the 62 subjects with data available, the median endometrium thickness was 9.0 mm (range 3-21 mm), and 2 (3.2%) subjects had thickness >16 mm. At visit III (10-18 days after the start of menses following treatment course 8), for the 49 subjects with data available, the median endometrium thickness was 7.0 mm (range 3-23 mm), and 1 (2.0%) subject had thickness >16 mm. At visit IV (follow-up visit approximately 3 months after last dose of ulipristal), for the 53 subjects with data available, the median endometrium thickness remained at 7.0 mm (range 1-16 mm), and no subjects had thickness >16 mm.

Endometrium histology

Endometrium biopsy samples were evaluated by the same 3 independent pathologists in study PGL11-024, as performed for studies PGL09-026 and PGL09-027. A consensus diagnosis of benign endometrium was made for all (100%) endometrium biopsy samples adequate for histology review, taken from screening of study PGL09-026 (96.2% adequate biopsies) through to visit IV of study PGL11-024 (91.7% adequate biopsies). All 3 individual pathologists provided a diagnosis of benign endometrium in all evaluations with the exception of one observation of complex, non-atypical, hyperplasia seen in one biopsy taken following treatment course 4 in PGL09-027, and not seen subsequently in individual biopsy assessments.

Summaries of non-physiological changes observed by at least 2 of the 3 pathologists suggested that after screening, when non-physiological changes were observed in 18.0% of biopsies, the

incidence in the full study population was highest in biopsies taken following treatment course 1, seen in 35.0% of biopsies, and then subsequently decreased. Following treatment course 4, at least 2 pathologists observed non-physiological changes in 21.4% of biopsies. Ten to18 days after the first menstruation following treatment course 8) non-physiological changes were observed in 16.3% of biopsies, which is comparable to baseline frequency (Table 15).

Table 15. Percentage of non-physiological changes diagnosed by at least 2 out of 3 pathologists in adequate biopsies in study PGL11-024.

Study		PGL09-026 Pearl III	PGL09-027 Pearl III ext.	PGL11-024 Pearl ext 2	PGL11-006 Pearl IV	
Doses N=Subjects exposed		10 mg N=209	10 mg (N=131)	10mg (N= 64)	5 mg N=230	10 mg N=221
At screening	%	10.9	(10.5)	(18.0)	7.8	8.4
3-month exposure	%	25.6	-		-	-
3-6 m after 3-month exposure	%	2.6	-		-	-
2 x 3-month exposure (i.e. approx. 9 months in the study)	%	-	50.0[b]		16.3	19.2
4 x 3-month exposure (i.e. approx. 18 months in the study)	%	-	25.3		16.2	10.3
3 months after 4 x 3-month exposure (i.e. approx. 21 months in the study)	%	-	22.8[c]	(15.2)	9.0	6.3
8 x 3 month exposure (i.e. approx. 39 months in the study)	% (n)			16.3 (43 adequate biopsies)		
3 months after 8 x 3-month exposure (i.e. approx. 42 months in the study)	% (n)			9.1[c] (22 adequate biopsies)		

a   taken under treatment with ulipristal acetate.
b   includes only a subset of subjects, as biopsy was performed if endometrium was thickened > 18m

c   includes only a subset of subjects, as biopsy was performed if non-physiological findings were reported by at least one pathologist after 4 (Study PGL09-027) or 8 (Study PGL11-024) treatment courses.

Source: 2.7.4-132; CSR PGL09-026 Table 44 and Table 14.3.11.3; PGL09-027, Table 14.3.11.3; PGL11-006, Table 14.3.10.4; PGL11-006 CSR Table 57, PGL11-024 Table 36

At follow-up visit biopsies were to be performed only if 1 or more pathologists had provided a diagnosis other than "benign physiologic endometrium" for the biopsy at visit III or if the biopsy was judged to be not adequate for histology review. A follow-up additional biopsy was provided by 24 subjects at visit IV, and 22 biopsies were considered adequate for review. In this subgroup, non-physiological changes were observed by at least 2 pathologists in 9.1% of biopsies. However, taking into consideration that for more than half of all subjects no follow-up biopsy had been requested due to a diagnosis of "benign endometrium" from all 3 pathologists at visit III, the observation of non-physiological changes in the full study population decreased to <5%, which is below baseline frequency and confirms the previously described rapid reversibility of non-physiological changes once treatment is stopped and menstruation returns.

Quality of life, pain and overall satisfaction were also evaluated during the study (Study PGL11-024). Overall, pain, assessed by VAS, was substantially reduced from baseline during the study and this reduction was sustained until the PGL11-024 follow-up visit 3 months after end of treatment. In the UFS-QoL assessment, the average symptom severity score showed an improvement (decrease) at the end of treatment course 1 in study PGL09-026, with a mean (median) change from baseline of 35.86 (40.63). This improvement was maintained following treatment courses 2, 3 and 4 in study PGL09-027. The improvement from baseline was less on average at the follow-up visit in study PGL09-027, at 23.39 (21.88). During PGL11-024, mean (median) change from baseline was similar to seen following earlier treatment courses during PGL09-026 and PGL09-027. At 3 month follow-up the mean (median) change from baseline was -25.7 (-25.0). The pattern of improvement was similar for the HRQL scales (improvement demonstrated by increase).

Overall the symptom severity and pain were reduced and QoL is improved and some maintenance of the achieved effect was demonstrated during treatment free intervals.

In summary, this extension study PGL11-024 has demonstrated that the intermittent administration of an additional 4 treatment courses of ulipristal 10 mg once daily for 3 months with drug-free intervals, bringing the total number of ulipristal treatment courses undertaken to 8, is well tolerated in women of reproductive age with symptomatic uterine myoma (studies PGL09-026, PGL09-027 and PGL11-024). Repetition of ulipristal treatment courses did not lead to any changes of concern in endometrial histology, nor to increases in endometrial thickness. The frequency of non-physiological changes observed did not increase with repeated treatment courses and, as previously demonstrated, non-physiological changes were rapidly reversible. Control of fibroid symptoms, uterine bleeding and overall satisfaction showed that, on average, subjects were very satisfied with the treatment and this satisfaction was maintained throughout the study and up to 3 months following the end of the eighth treatment course. In addition, an important improvement in quality of life was observed following the first treatment course which was sustained thereafter over the 8 treatment courses until study follow-up, reaching scores reported for healthy individuals.

12.2.2.   Evaluator comment

There are no long-term follow up data available for the patients completing the 4 courses of UPA treatment in Study PGL11-006.

The Sponsor has provided the Clinical Study Report for Study PGL11-024, an optional open-label extension study to assess the efficacy and safety of an additional 4 intermittent 3-month courses of UPA for those subjects completing 4 treatment courses in Studies PGL09-026 and PGL09-027.

There were 64 patients who continued in to Study PGL11-024, with 53 (82.8%) of subjects completing the study and attending the follow-up visit. Subjects received UPA 10 mg daily for 3 months (84 days) followed by a treatment free interval until the start of second menses following previous treatment course; it is noted NETA was not administered in this extension study.

The primary objective was to assess patient satisfaction with receiving repeated intermittent UPA treatment courses (myoma symptom control assessed using Global Study Treatment Satisfaction Questionnaire [GSTSQ]). Secondary objectives included assessment of efficacy (myoma size) and long-term safety with respect to the endometrium and AEs.

12.2.2.1. Efficacy

In terms of myoma volume, the mean (median) percent CFS in total volume of the 3 largest myomas (FAS population) at the end of treatment course 4 (in Study PGL09-027) was -56.6 (-77.3)%, and -28.5 (-67.1)% at the end of treatment course 8. At the 3 month post-treatment follow-up the mean (median) percent CFS in total myoma volume was -15.2 (-70.3)%. The Sponsor notes the difference in mean and median values, commenting that at least 3 subjects had an increase in myoma volume at the Study PGL11-024 study visits, with a larger influence on the mean than median values. Overall, the percentage of subjects with a reduction of myoma volume of ≥ 25% and ≥ 50% from screening was comparable at 3 months follow-up after 4 treatment courses (73.0% and 61.9% respectively [Study PGL09-027] and at 3 months follow-up after 8 treatment courses (76.5% and 66.7% respectively).

The PBAC was recorded for days 1-8 of the first menstruation at the re-start of treatment in PGL11-024 only. The mean (median) change from first menses post screening (Study PGL09-026) PBAC score was -129.9 (-88.5). Otherwise uterine bleeding was assessed by the GSTSQ, which comprised of the following 4 questions:

- How satisfied or dissatisfied are you with the ability of the study drug to prevent or treat your fibroid symptoms?

- How satisfied or dissatisfied are you with the way the study drug relieves the uterine bleeding due to your fibroids symptoms?

- Taking all things into account, how satisfied or dissatisfied are you with this study drug?

- How do you estimate your menstrual bleeding now compared to before the very first intake of this study drug?

The primary efficacy endpoint was myoma symptom control assessed by the average score of the responses to the first 3 questions of the GSTSQ (graded from 1 = extremely satisfied to 7 = extremely dissatisfied) at visits II (10-18 days after start of menses following treatment course 6) and III (10-18 days after start of menses following treatment course 8). The mean (interquartile range) response at visit III was 1.93 (1.00, 2.67), demonstrating subjects were generally very satisfied with treatment; similar results were observed at other study time points.

It is noted there were 4 (6.3%) subjects who underwent surgery during Study PGL11-024; the main reason for surgery reported as 'insufficient efficacy of treatment (n = 3) and 'other: abdominal hysterectomy' (n = 1).

12.2.2.2. Safety

Those subjects completing PGL11-024 were study participants for approximately 4 years (PGL09-026 commencing July 2010, and PGL11-024 completed March 2015). Overall, 73.4% of subjects reported at least one on-treatment TEAE during treatment courses 1-8, most frequently during treatment course 1 (50.0%; Study PGL09-026). The most frequent on-treatment TEAEs reported were nasopharyngitis, hot flush and headache, consistent with the AE profile of UPA reported at Round 1. There were no deaths or SAEs reported in Study PGL11-024.

Endometrial biopsies were collected for all subjects at visit III (10-18 days after start of menstruation following treatment course 8) and evaluated by the same 3 independent pathologists from Studies PGL09-026 and PGL09-027. A consensus diagnosis of benign

endometrium was reported for all endometrial samples considered adequate for histology review in Study PGL11-024; it is noted there were one case of complex, non-atypical hyperplasia reported following treatment course 4 (PGL09-027), although this was not seen on subsequent biopsy assessment. At the follow up visit (3 months after last dose of treatment course 8), there were no subjects with an endometrial thickness > 16 mm.

Non-physiological changes were reported by at least 2 pathologists for 16.3% of biopsies at visit III (43 adequate biopsies), and for 9.1% at visit IV (3 months after treatment course 8). It is noted there were 24 biopsies (22 adequate for histology review) at visit IV as biopsy was only performed if 1 or more pathologist reported non-physiological changes at visit III, or the visit III biopsy was inadequate for histology review.

Overall, there are no new safety concerns identified in this study, however, the number of subjects is too small to draw firm conclusions regarding endometrial safety with 8 intermittent UPA treatment courses.

Of note, the CHMP Evaluation of Study PGL11-024 was received by the TGA during the Round 2 Evaluation stage. The Sponsor proposed changes to update the current sentence in Section 4.4 Warnings to include 8 courses and to delete the similar sentence in Section 4.2 Posology.

The CHMP Rapporteur stated "*In conclusion, although data related to endometrial safety after eight courses of intermittent use are considered reassuring, they are very limited and relate only to use of the non-approved 10 mg tablet. For that reason the proposed rewording of the SmPC in section 4.2 and 4.4 is currently not recommended for approval*."

The Co-Rapporteur stated further "*The conclusions on efficacy based on the additional results collected on 53 women who received ulipristal 10 mg up to 8th treatment cycles are endorsed. Regarding safety, we do consider that the 10 mg data can be extrapolated to the 5 mg, but the limited number of women needs further discussion.*

Regarding the SmPC, we propose to maintain the current text. The proposal to mention the limited number of women who have been treated for 8 intermittent course in section 4.2 and additional information on section 4.8 is not supported until this discussion has taken place. If acceptable, additional information should be included in section 5.1 with a reference in section 4. 2."

There was no change proposed to the safety specification, although the Delegate's attention is drawn to the updated Pharmacovigilance plan in the revised RMP submitted to the EMA.

12.3. Question 3

- 3. The GnRH agonist leuprorelin is not registered in Australia for use in the management of uterine fibroids, although goserelin 3.6 mg is registered for this indication. The Clinical Expert stated in the Clinical Overview "the two GnRH agonists being similar, the active comparator selected in the study PGL07-022 and study findings are thus appropriate to conclude about the benefit of Esmya over medical therapies currently registered in Australia to manage uterine fibroids".

  Please provide further information to justify the statement "the two GnRH agonists being similar".

12.3.1. Sponsor's response

GnRH agonists (GnRHa) are synthetic peptides structurally similar to the native GnRH. Like native GnRH, all GnRHa molecules interact with the GnRH receptor to elicit its biological actions. GnRHa molecules have greater potency and a longer half-life than native GnRH. GnRHa continuously stimulate the receptor, and this prolonged exposure results in a down-regulation effect and subsequent hypogonadism that in turn induces a state of hypoestrogenism (by suppressing pituitary ovarian functions), which has been used as a treatment for fibroids

(Lethaby 2011). Many trials have demonstrated that pre-operative administration of GnRHa for a duration of 3 to 6 months decreases uterine and fibroid size and has beneficial effects on perioperative outcomes, notably through normalization of haemoglobin levels prior to surgery.

Lupron depot/Enantone depot (leuprolide acetate for depot suspension) was approved by many regulatory agencies worldwide for the short term (maximum 6 months) medical treatment of uterine fibroid. The leuprorelin 3.75 mg injection was used as an active comparator in study PGL07-022. In Australia, the GnRH agonist goserelin is approved for short term treatment of uterine myoma as an adjunct to surgery in the form of an implant dosed 3.6 mg. A direct comparative trial (Lim et al 2008) showed that both molecules had strictly similar effects on fibroid and uterine size, exactly similar safety profiles, and same beneficial effect on perioperative outcomes. The study concludes that both can be equally chosen for this pre-operative adjunctive therapy, depending on local accessibility and price. In the 2011 Cochrane review on pre-operative use of GnRHa for uterine fibroids, 7 studies using leuprorelin 3.75 mg and 7 studies using goserelin 3.60mg were included, showing similar efficacy (bleeding, fibroid and uterine volume, Hb, Ht) on pre-operative end-points.

Despite some pharmacokinetic differences, the biological and clinical effects of the 2 molecules are strictly similar in women with uterine fibroids. It is therefore considered that study PGL07-022 comparative results vs. ulipristal acetate 5 and 10 mg would also apply to a medical treatment with goserelin acetate 3.6 mg.

In conclusion, there is clear evidence from randomised trials that the use of GnRH analogues is associated with a significant reduction in uterine volume and fibroid size (Lethaby 2011), in that regard all the GnRH analogues which have been studied in that indication seem to have very similar effect on efficacy parameters.

12.3.2. Evaluator comment

The Sponsor's response is noted and considered acceptable.

12.4. Question 4

- 4. Given Study PGL-W-001 was not considered conclusive regarding use in moderate hepatic impairment, are further studies planned to assess the use of ulipristal acetate in women with hepatic impairment?

12.4.1. Sponsor's response

No further studies are planned to assess the use of ulipristal acetate in women with hepatic impairment. The proposed Product Information terms reflect the necessary precautions to be applied in this specific population:

> *Hepatic impairment*
>
> *There is no therapeutic experience with ulipristal acetate in patients with hepatic impairment. Hepatic impairment is expected to alter the elimination of ulipristal acetate, resulting in increased exposure. This is considered not to be clinically relevant for patients with mildly impaired liver function. Ulipristal acetate is not recommended for use in patients with moderate or severe hepatic impairment unless the patient is closely monitored.*

12.4.2. Evaluator comment

The Sponsor's response is noted; the information provided in the PI regarding hepatic impairment is considered acceptable.

12.5. Question 5

- 5. Regarding Study PGL11-006, please provide regarding the frequency of treatment related adverse events related to excessive uterine bleeding for subjects in Study PGL11-006 during and after ulipristal acetate treatment course 3 and treatment course 4.

12.5.1. Sponsor's response

According to data presented, the frequency of TEAEs related to excessive bleeding did not increase with the number of treatment courses or with the daily dose in study PGL11-006 as TEAEs were reported in:

- 6 [3.1%] subjects during or after treatment course 3 (in 2 [1%] subjects the TEAEs were considered related to treatment) and 4 [2.2%] subjects during or after treatment course 4 (none were considered related to treatment) in the 5 mg group.

- 4 [2.1%] subjects during or after treatment course 3 (in 3 [1.6%] subjects the TEAEs were considered related to treatment) and 3 [1.7%] subjects during or after treatment course 4 (in 1 [0.6%] subject the TEAE was considered related to treatment) in the 10 mg group.

12.5.2. Evaluator comment

The Sponsor's response is noted and considered acceptable. TEAE's related to excessive uterine bleeding were similar to those reported during treatment course 1 and after treatment course 2:

- 3.5% (5 mg group) and 1.8% (10 mg group) during treatment course 1.
- 3.2% (5 mg group) and 2.0% (10 mg group) after treatment course 2.
- 3.1% (5 mg group) and 2.1% (10 mg group) during or after treatment course 3.
- 2.2% (5 mg group) and 1.7% (10 mg group) during or after treatment course 4.

13. Second round benefit-risk assessment

13.1. Second round assessment of benefits

After consideration of the responses to clinical questions, the benefits of ulipristal acetate in the proposed usage are unchanged from those identified in Round 1.

13.2. Second round assessment of risks

After consideration of the responses to clinical questions, the risks of ulipristal acetate in the proposed usage are:

- Endometrial safety - further to comments in Section 9.2 above, whilst there are data from a small number of women exposed to 8 intermittent treatment courses, essentially long-term data on endometrial safety are lacking. A key consideration therefore is appropriate monitoring and follow-up of patients using repeated intermittent ulipristal acetate treatment. The Sponsor has provided the proposed education materials as part of the S31 response; adequacy of the prescriber and pathologist education material is subject to expert clinical advice. A further issue for discussion is whether use of ulipristal acetate should be restricted to specialists pending availability of longer term endometrial safety data.

13.3. Second round assessment of benefit-risk balance

The benefit-risk balance of ulipristal acetate 5 mg tablets, given the proposed usage, is uncertain due to the lack of long-term safety data.

14. Second round recommendation regarding authorisation

Based on the data provided, there is no reason to reject the application to extend the indication for ulipristal acetate on efficacy grounds. However, given the lack of long-term safety data, external expert clinical advice as to whether duration of treatment should be included in the proposed indication 'Ulipristal acetate is indicated for intermittent treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age' is sought.

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