EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

15 December 2011

EMA/486902/2018
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Esmya

ulipristal

Procedure No.: EMEA/H/C/002041//0000

Note

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

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Product information

Name of the medicinal product:	Esmya
Applicant:	PregLem France SAS. 32, route de l'Eglise F-74140 Massongy France
Active substance:	ulipristal acetate
International Non-proprietary Name:	ulipristal
Pharmaco-therapeutic group (ATC Code):	Uterine myoma
Therapeutic indication(s):	Ulipristal acetate is indicated for pre-operative treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age. The duration of treatment is limited to 3 months (see section 4.4)
Pharmaceutical form:	Tablet
Strength:	5 mg
Route of administration:	Oral use
Packaging:	PVC/PE/PVDC/Alu blisters
Package size:	28 tablets

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List of abbreviations

AAS	Atomic Absorption Spectrometry
ACTH	Adrenocorticotropic hormone
ADME	Absorption, Distribution, Metabolism and Elimination
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse Event of Special Interest
ALAT	Alanine aminotransferase
ALP	Alkaline phosphatase
AP	Applicant's Part (or Open Part) of a DMF
API	Active Pharmaceutical Ingredient
AR	Assessment Report
ASM	Active Substance Manufacturer
ASMF	Active Substance Master File = Drug Master File
ASR	Annual Safety Report
AST	Asparate Transaminase
ASV	Aqueous suspending vehicle
AUC	Area under the curve
BMI	Body mass index
BP	British Pharmacopoeia
CEP	Certificate of Suitability of the European Pharmacopoeia
CFU	Colony Forming Units
CHMP	Committee for Medicinal Product for Human Use
C_{max}	Maximum concentration
CMS	Concerned Member State
CoA	Certificate of Analysis
CPK	Creatine phosphokinase
CRS	Chemical Reference Substance (official standard)
CT	Computed Tomography
DCM	Dichloromethane
DB	Double Blind
D&C	Dilation and Curettage
DDI	Drug-Drug Interaction
DILI	Drug Induced Liver Injury
DMF	Drug Master File = Active Substance Master File
DP	Decentralised (Application) Procedure
DSC	Differential Scanning Calorimetry
E2	Estradiol
ECG	Electrocardiogram
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
EMA	European Medicines Agency
EU-RMP	European Risk Management Plan
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GLP	Good laboratory practice
GMP	Good manufacturing practice
GnRH	Gonadotropin releasing hormone
GPRD	General Practice Research Database
Hb	Hemoglobin
Hct	Hematocrit
HDPE	High Density Polyethylene IPCIn-process control
HERG	Human ether-a-go-go gene
ICH	International Conference on Harmonisation
IND	Investigational new drug
INN	International Non proprietary Name
IR	Infrared
ITT	Intent-to-treat
IU	International Units

IUD	Intrauterine Device
JP	Japanese Pharmacopoeia
LCL	Lower confidence limit
LC-MS /MS	Liquid chromatography tandem mass spectrometry
LDH	Lactate dehydrogenase
LDPE	Low Density Polyethylene
LH	Luteinising Hormone
LLT	Lower Level Term
LOA	Letter of Access
LOD	Limit of Detection
LOQ	(1) Limit of Quantification, (2) List of Questions
MA	Marketing Authorisation
MAH	Marketing Authorisation holder
MD	Multiple Dose
MEB	Medicines Evaluation Board
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
MS	Mass Spectrometry
ND	Not detected
NICE	National Institute of Health and Clinical Excellence
NICHD	National Institute of Child Health and Human Development
NIH	National Institutes of Health
NLT	Not less than
NMR	Nuclear Magnetic Resonance
NMT	Not more than
NOEL	No observed effect level
OOS	Out of Specifications
P4	Progesterone
PAEC	Progesterone Receptor Modulator Associated Endometrial Changes
PB	Population Based
PBAC	Pictorial Bleeding Assessment Chart
PD	Pharmacodynamic
PDE	Permitted Daily Exposure
PE	Polyethylene
Ph.Eur.	European Pharmacopoeia
PIL	Patient Information Leaflet
PIP	Paediatric investigational plan
PK	Pharmacokinetic
PL	Patient Leaflet
p.o.	per os (oral)
PP	Per-protocol
PR	Progesterone receptor
PR-A	Progesterone receptor isoform A
PR-B	Progesterone receptor isoform B
PRM	Progesterone Receptor Modulator
PSUR	Periodic Safety Update Report
PT	Prothrombin Time
PVC	Poly vinyl chloride
QD	Quality Development
QoL	Quality of Life
QOS	Quality Overall Summary
RBA	Relative binding affinity
RIA	Radioimmunoassay
RH	Relative Humidity
RMP	Risk Management Plan
RMS	Reference Member State
RP	Restricted Part (or Closed Part) of a DMF
RRT	Relative retention time
RSD	Relative standard deviation
RTI	Research Triangle Institute
RVG #	Marketing Authorisation number in NL
SAE	Serious adverse event

s.c.	subcutaneous
SD	Standard deviation
SF-MPQ	Short Form McGill Pain Questionnaire
SOC	System organ class
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA Query
SOC	System organ class
SPRM	Selective Progesterone Receptor Modulator
$t_{½}$	half-life
TEAE	Treatment emergent adverse event
TGA	Thermo-Gravimetric Analysis
T_{max}	Time of maximum concentration
TSH	Thyroid-stimulating hormone
UAE	Uterine Artery Embolisation
UFS-QoL	Uterine Fibroid Symptom and Health-Related Quality of Life Questionnaire
ULN	Upper Limit of Normal Range
UV	Ultraviolet
USP/NF	United States Pharmacopoeia/National Formulary
VAS	Visual analog scale
VEGF	Vascular endothelial growth factor
WHO	World Health Organization
XRD	X-Ray Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant PregLem France S.A.S. submitted on 19 November 2010 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Esmya, through the centralised procedure under Article 3(2) (a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 29 September 2009.

The applicant initially applied for the following indication: treatment of symptoms (heavy uterine bleeding and/or pain) in patients with uterine fibroids who are eligible for surgery, or when surgery is not appropriate. Esmya is indicated in pre-menopausal adult women. Subsequently, the indication was revised as follows: Ulipristal acetate is indicated for pre-operative treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age. The duration of treatment is limited to 3 months (see section 4.4)

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

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

Information relating to orphan market exclusivity

Similarity

Not applicable.

Applicant's request for consideration

Additional data/ market exclusivity

The applicant requested consideration of one year data/market exclusivity in regards of its application for a new indication in accordance with Article 14(11) of Regulation (EC) 726/2004.

Scientific Advice

The applicant did not seek scientific advice at the CHMP.

Licensing status

The product Esmya was not licensed in any country at the time of submission of the application.

Another product containing the same active substance, Ellaone (ulipristal acetate) was authorised in the EU on 15 May 2009 in the indication of emergency contraception within 120 hours (5 days) of unprotected sexual intercourse or contraceptive failure. The marketing authorisation holder for Ellaone is Laboratoire HRA Pharma.

HRA Pharma and PregLem France S.A.S are distinct companies but have entered licensing agreements for ulipristal acetate therefore the concept of Global Marketing Authorisation applies.

1.2. Steps taken for the assessment of the product

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

Rapporteur: **Tomas Salmonson** Co-Rapporteur: **Pieter de Graeff**

- The application was received by the EMA on 19 November 2010.
- The procedure started on 15 December 2010.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 7 March 2011. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 4 March 2011.
- During the meeting on 11-14 April 2011, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 14 April 2011.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 19 May 2011.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 5 July 2011.
- During the CHMP meeting on 21 July 2011, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 22 August 2011.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 5 September 2011.
- During the CHMP meeting on 22 September 2011, the CHMP agreed on a second list of outstanding issues to be addressed by the applicant.
- The applicant submitted the responses to the second CHMP List of Outstanding Issues on 17 October 2011.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the second List of Outstanding Issues to all CHMP members on 1 November 2011.
- During the CHMP meeting on 17 November 2011, the CHMP agreed on a third list of outstanding issues to be addressed by the applicant.
- The applicant submitted the responses to the third CHMP List of Outstanding Issues on 17 November 2011
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the third List of Outstanding Issues to all CHMP members on 28 November 2011.

- During the meeting on 12-15 December 2011, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Esmya on 15 December 2011.

2. Scientific discussion

2.1. Introduction

Uterine fibroids

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

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

Treatment

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

Because uterine fibroids are hormone dependent and often regress after menopause, suppression of circulating oestrogen has been applied as a medical approach for treating fibroids. Gonadotropin releasing hormone (GnRH)-agonists are therefore licensed for the pre-operative treatment of symptomatic uterine fibroids. GnRH-agonists are effective in reducing fibroid-related bleeding, correcting anaemia when given concomitantly with iron therapy, reducing abdominal symptoms and reducing fibroid and uterine volume. Their use is limited to 3-6 months duration as suppression of oestrogen to castration levels results in menopausal symptoms including hot flushes, mood swings and loss of libido and can also lead to loss of bone mineral density.

About the product

Esmya (Ulipristal acetate) is a progesterone receptor antagonist. It acts by depriving uterine fibroids of growth stimulation due to progesterone. Ulipristal acetate is indicated for pre-operative treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age. The duration of treatment is limited to 3 months.

The treatment consists of one tablet of 5 mg to be taken orally once daily for up to 3 months, and it should be started during the first week of a menstrual cycle. There are no data available on treatment with a duration longer than 3 months or on repeat courses of treatment. Therefore, treatment duration should not exceed 3 months.

2.2. Quality aspects

2.2.1. Introduction

Esmya contains the active substance ulipristal acetate. For other ingredients see the SmPC. The product is formulated as immediate-release, white to off-white round biconvex 5 mg tablets, which are embossed by “ES5” on one side.

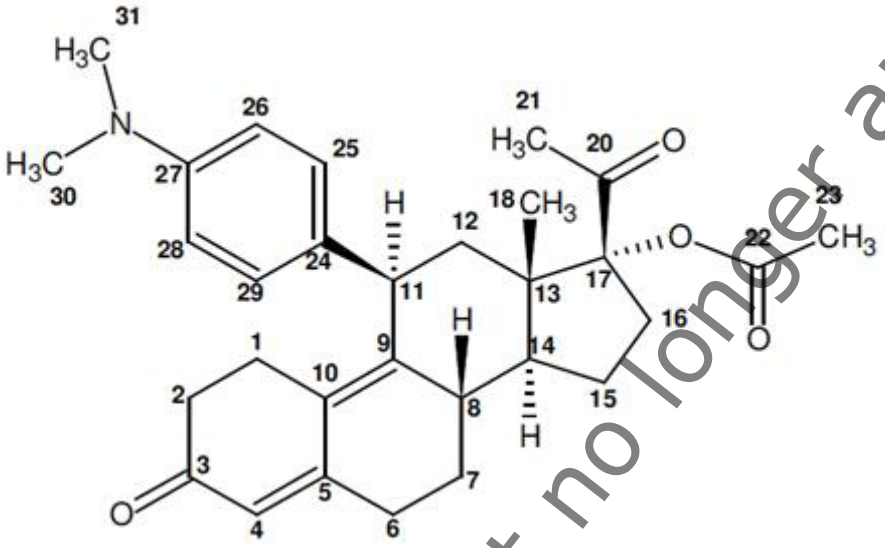
The product is packaged in orange PVC/PE/PVDC/Alu transparent triplex blisters.

2.2.2. Active Substance

The chemical name of the active substance is 17α-Acetoxy-11β-(4-N,N-dimethylaminophenyl)-19-norpregna-4,9-diene-3,20-dione.

The corresponding molecular formula is $C_{30}H_{37}NO_4$, molecular weight is 475.619 g/mol.

The absolute configuration of the chiral centers is as follows: 8S, 11R, 13S, 14S, 17R.



Ulipristal acetate is a white to yellow crystalline powder. It is freely soluble in methylene chloride, soluble in methanol, acetone and ethanol and insoluble in water. The desired particle size is achieved by micronisation The substance does not show polymorphism, which has been confirmed by a number of studies.

An ASMF procedure is used to provide information on the active substance.

Manufacture

The structure elucidation of ulipristal acetate was performed with Elemental Analysis, Infra-Red (IR) spectroscopy, Nuclear Magnetic Resonance (NMR) (1H-NMR and 13C-NMR, HMBC, HMQC and COSY), UV spectroscopy and mass spectroscopy. The polymorphic form of ulipristal acetate is also characterized by differential scanning calorimetry (DSC), IR and X-ray diffraction. The validation-production batches of ulipristal acetate have been analysed by IR, DSC and X-ray diffraction in order to confirm that the active substance ulipristal acetate presents a homogenous crystalline structure, when obtained following the proposed synthetic process. In conclusion, the drug substance exists in one polymorphic form.

Analyses of chromatographic purity by HPLC, assay and optical rotation in the final product confirm the exact chiral structure of the active.

Specification

Control tests for the active substance include description, identification by IR spectrum and HPLC, related substances and assay by HPLC, optical rotation, melting point, water content, heavy metals, residual solvents and particle size.

The acceptance criteria for impurities, including limits for organic impurities, inorganic impurities and residual solvents, are defined. Origin of the impurities and amounts found in clinical trials are described. As confirmed by numerous studies, none of the impurities are genotoxic. Impurity limits in the specification are justified and found safe.

The limits for residual solvents are those of the Ph.Eur. monograph or tighter.

The limits set for specification parameters are acceptable and in line with batch results, stability studies and CHMP guidelines. Analytical methods used are sufficiently described and fully validated in line with the CHMP requirements.

Results of analysis of six production batches of the active substance were provided. Compliance with the specification was demonstrated.

Stability

Stability studies have started for 6 validation batches at both accelerated (40°C/75% RH) and long-term (25°C/60% RH) conditions. Testing frequencies are according to valid guidelines and the following parameters are monitored: description, identification by IR, water content, related substances and assay by HPLC and optical rotation. The same limits as those proposed for release are used.

Accelerated studies have been completed for all batches. Long-term results are available from 9 to 60 months, depending on the individual batch manufacturing date.

Forced degradation studies have been carried out to study degradation patterns of the active substance and to confirm that the HPLC method is stability indicating. The degradation was low in most conditions but almost total in hard oxidizing conditions and at pH 14. Specified impurities were detected in heat, acid and basic conditions, respectively. Unknown impurities were detected in strong heat and strong basic conditions.

A photostability study was also performed according to ICH Q1B conditions. Degradation was found in both solid drug substance and in drug substance in solution. It can be concluded that ulipristal acetate is light sensitive.

A suitably validated re-test period is approved, supported by the available stability data. The active substance should be stored protected from light; no other storage precautions are needed.

2.2.3. Finished Medicinal Product

The product is formulated as immediate-release, white to off-white round biconvex 5 mg tablets, which are embossed by “ES5” on one side.

The excipients used in the tablets are all standard pharmaceutical grade excipients that correspond to the appropriate Ph.Eur. monographs. Microcrystalline cellulose and mannitol are included as diluents, croscarmellose sodium as a disintegrant, talc as a glidant and lubricant that prevents sticking upon compression and magnesium stearate also as a lubricant.

Adventitious agents

All excipients are either of synthetic or vegetable origin. The magnesium stearate is of vegetable origin and a statement confirming this is provided from the supplier.

Manufacture of the product

The manufacturing process of the finished product was sufficiently described. Process validation studies were performed on two pilot batches and three validation batches. The data demonstrate that the process is well controlled and the finished product complies with the specification. In addition, process validation scheme for commercial scale batches, which addresses all requirements from the validation guideline (CPMP/QWP/848/96), was presented. Therefore, process validation was found to be adequate in combination with the process validation scheme for larger batch sizes. Process validation for the commercial size batches will be carried out before release on the market.

Product specification

The specification of the finished products includes standard testing parameters for this kind of dosage form. The finished product is tested for appearance, identity by TLC and HPLC, related substances and assay by HPLC, disintegration, dissolution, average mass, content uniformity and microbial purity. The shelf-life limits for assay and impurities were tightened during the procedure. Impurities/degradation products were evaluated and found to be acceptable from the safety perspective.

All the analytical tests used for the finished product control were sufficiently described and appropriately validated.

Batch analysis results of seven batches (clinical, development, stability and validation batches) were presented. All batches comply with the finished product specification.

Stability of the product

Stability studies were started for the product packaged in the proposed commercial packaging, orange PVC/PE/PVDC/Alu transparent triplex blisters on commercial scale batches. Full commercial scale batches will be also placed on stability once available.

The parameters tested are appearance, related substances, assay, dissolution, disintegration, average mass and microbial purity. Testing frequency corresponds with the current guideline requirements.

Results of accelerated studies at 40°C/75% RH up to 6 months and results of long-term studies at 25°C/60% RH up to 24 months are available. Only very little degradation is observed and no new degradation products are seen. Changes in assay, average mass and dissolution are not significant. All results comply with the acceptance criteria at the end of shelf-life.

In general, the results support the shelf-life and storage conditions as defined in the SmPC.

GMO

N/A

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

No quality-related major objections were raised during the assessment time. All other concerns were addressed satisfactorily by the applicant in the response package. The information presented in the quality dossier is considered satisfactory and adequate to support the marketing authorisation.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the drug substance and drug product have been presented in a satisfactory manner. The results of tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.

2.3. Non-clinical aspects

2.3.1. Introduction

The non-clinical development program, except in a limited number of specific cases, was conducted in female animals. Safety pharmacology, general toxicology, genotoxicity and reproduction toxicology studies with ulipristal acetate were performed in accordance with Good Laboratory Practices (GLP).

2.3.2. Pharmacology

Progesterone plays a pivotal role in reproduction. It is involved in the control of ovulation, implantation, and maintenance of pregnancy, and withdrawal of progesterone at the end of a non-fertile cycle results in menstruation in humans and nonhuman primates. In the uterus, progesterone controls the growth and differentiation of endometrial and myometrial cells and directly regulates a variety of cell functions; it also acts indirectly by functionally opposing various estrogen effects. In the non-pregnant uterus, progesterone exerts both inhibitory and stimulatory effects on cell proliferation in a cell- and tissue-specific manner.

Progesterone mediates its physiological effects through interaction with the progesterone receptor, a member of the superfamily of nuclear receptors. The recognition of the important role of progesterone in reproduction led to the development of synthetic progesterone receptor ligands, also known as Selective Progesterone Receptor Modulators (SPRMs). The synthesis of mifepristone (RU486), the first progesterone and glucocorticoid receptor antagonist, was a starting point of drug discovery for progesterone receptor modulators throughout the world, with much attention focused on finding compounds with increased progesterone antagonistic potency and reduced antiglucocorticoid activity compared with mifepristone. Ulipristal acetate, which binds strongly to the progesterone receptor and stabilizes it in an antagonist conformation and inhibits progesterone induced transcription, is a result of this search.

SPRMs have been shown to work through several mechanisms of action in uterine fibroids. Firstly they interact with the progesterone receptors in the fibroid cells triggering apoptosis and inhibiting proliferation of these cells. Secondly, SPRMs display a direct and specific effect on the endometrium, stopping bleeding within a few days. Thirdly, they reduce gonadotrophin secretion and inhibit ovulation while maintaining serum estrogen levels at moderate concentration corresponding to mid follicular phase levels.

Primary pharmacodynamic studies

The binding of ulipristal acetate to hormonal steroid receptors has been studied in a number of reports with the data being expressed either as an IC_{50} or as Relative Binding Affinity (RBA) as compared to a value of 100% for reference agent (progesterone for the progesterone receptor, dexamethasone for the glucocorticoid receptor, estradiol for the estrogen receptor, dihydrotestosterone or methyltrienolone for the androgen receptor).

In vitro studies

A summary of studies performed *in vitro* with can be found in the table below.

Table 1. Summary of primary pharmacodynamic studies performed *in vitro* with ulipristal acetate.

Type of Study, report	TEST SYSTEM	Test conditions	Conclusion
Steroid receptor binding, *in vitro* **PGL-H-401**	Extracts from rat uterus, prostate and thymus extracts, rabbit uterus, human IM9 cells	Comparison of binding of ulipristal acetate and mifepristone to various steroid receptors.	Ulipristal acetate is a progesterone receptor antagonist and also a glucocorticoid receptor antagonist with little or no activity at the estrogen receptor. The pharmacodynamic profile is similar to that of mifepristone.
Steroid receptor binding and in vitro antiprogesterone activity **PGL-H-402**	Extracts from rabbit uterus and thymus, recombinant rat and human receptors. T47D-C) and HepG2 cells	Comparison of binding of ulipristal acetate and mifepristone to various steroid receptors.	Ulipristal acetate is an antiprogestine with similar potency as mifepristone.
Characterization of in vitro glucocorticoid receptor binding **PGL-H-403**	T47D and HeLa cells	Receptor binding to progesterone and glucocorticoid receptors. Progesterone agonist and antagonist activity was assessed through stimulation of alkaline phosphatase activity in T47D. Glucocorticoid antagonistic activity was assessed in HeLa cells.	Receptor binding studies showed K_d values of 0.58±0.03 and 0.31±0.04 nM for mifepristone and ulipristal acetate, respectively, on the progesterone receptor with corresponding values on the glucocorticoid receptor of 0.68±0.06 and 1.68±0.18 nM – reference values were 3.95±0.25 nM for progesterone and 9.5±1.5 nM for dexamethasone on the respective receptors. In T47D cells, ulipristal acetate and mifepristone functioned as pure antagonists at the progesterone receptor. At the glucocorticoid receptors, mifepristone functioned as a full antagonist while ulipristal acetate functioned as a competitive antagonist. see above
Leiomyoma cell proliferation, **PGL-H-410**	Human leiomyoma cells	In vitro 1, 10, 100, 1000 nM	Ulipristal acetate inhibits the proliferation of cultured leiomyoma cells by down-regulating PCNA expression and induces apoptosis by up-regulating cleaved caspase-3 and PARP expression and down-regulating Bcl-2 expression.
Leiomyoma cell protein expression, **PGL-H-411**	Human leiomyoma and normal myometrial cells	In vitro 10, 100, 1000 nM	Ulipristal acetate down-regulates VEGF, ADM and their receptor contents and moderates PR isoform contents in cultured leiomyoma cells in a cell-type specific manner.
Steroid receptor	Extracts from	Comparison of	The monodemethylated metabolite of ulipristal acetate

binding and in vitro antiprogesterone activity **PGL-H-449**	rabbit uterus and thymus, recombinant rat and human receptors. T47D-C) and HepG2 cells	binding of ulipristal acetate and mifepristone and their putative metabolites to various steroid receptors.	has similar pharmacodynamic activity compared to that of ulipristal acetate both at recombinant human progesterone-A and progesterone –B receptors and at rabbit progesterone and glucocorticoid receptors.
Endometrial cell proliferation, **PGL-H 460**	YHES cells	In vitro 0.1-100µM	Treatment of cell cultures with 100 µM ulipristal acetate significantly inhibited proliferation but lower concentrations were without effect; similar results were observed with mifepristone.

Pharmacodynamic activity of metabolites to ulipristal acetate

The pharmacological activity of the principal metabolites of ulipristal acetate, the mono-N-demethylated (PGL4002) and di-N-demethylated (PGL-4004) derivatives has been investigated through receptor binding in limited *in vitro* and *in vivo* programmes. *In vitro*, both PGL4002 and PGL4004 bound to progesterone receptors, with PGL4002 having the greater affinity. *In vivo*, PGL4002 showed activity in the anti-Clauberg test after oral administration, but this was less than that of ulipristal acetate (doses up to 1.6 mg/rat/day) while PGL4004 was only weakly active after intraluminal administration in the anti-McGinty test (dose of 1.0 µg, in a comparative study where 1.0 µg of ulipristal acetate gave 79.4% inhibition of endometrial proliferation) (PGL-H-450).

Secondary pharmacodynamic studies

The antiovulatory and antifertility (post-coital) activity of ulipristal acetate has been investigated in rats in several studies. Ulipristal acetate has a dose-dependent antiovulatory effect and completely blocked ovulation at and above doses of 2 mg/kg. A partial blockade of ovulation was noted already at the lowest dose 0.5 mg/kg. Mifepristone was partially active at 4 mg/kg and did not completely block ovulation even at the highest dose investigated, 8 mg/kg following oral administration. The antifertility or post-coital effect was investigated in female rats that were mated with fertile males and dosed on day 4 to 6 of gestation. The animals were euthanized on day 10 of gestation and the number of concepti was recorded. Ulipristal acetate at doses of 2.0 mg/rat/day, either p.o. or s.c., prevented pregnancy in all animals in the respective groups while 1 mg/kg had a partial post-coital effect. In another dosing regimen with single 2 mg doses of ulipristal acetate to rats on different days of mating, no post-coital effect was observed on days 0, 1, 2 or 3 post-mating, but prevented 100% of gestations on day 4 but with less effect on day 5. Administration of progesterone to ulipristal acetate treated pregnant rats reversed the post-coital antifertility effect and maintained pregnancy. A dose-dependent post-coital effect of ulipristal acetate was observed in rabbits when the animals were dosed on gestation days 0-3. A compete block of gestation was seen at 10 mg/kg and a partial block of gestation at 4 and 8 mg/kg. On days 4, 5 or 6, 32 mg/kg, had no or slight post-coital effect while 64 mg/kg totally blocked gestation in the rabbit.

The ability of ulipristal acetate to terminate pregnancies was investigated in the guinea-pig and monkey. Ulipristal acetate, mifepristone and lilopristone were approximately equipotent at the dose levels of 10 and 30 mg/day in terminating pregnancies in guinea-pigs when the animals were treated on days 43 and 44 of gestation. Pregnant long-tailed macaques (5/group) were administered ulipristal acetate or mifepristone 0.5 or 5 mg/kg/day p.o. or 0.5 mg/kg/day i.m. on days 23-26 of gestation. Pregnant animals were assessed by ultrasound pre-treatment (day 23) and then monitored on days 26-28, 30, 32, 35, 55, 80, 100, 130 and 145. At 0.5 mg/kg of ulipristal acetate there was no loss of

foetuses, while at 5 mg/kg 2/5 foetuses were lost. The corresponding figures for mifepristone is 2/5 foetuses lost at 0.5 mg/kg while 4/5 foetuses were lost at 5 mg/kg following oral administration. When using intramuscular administration of 0.5 mg/kg 4/5 foetuses were lost in ulipristal acetate treated animals and 3/5 in mifepristone treated animals. In monkeys in which pregnancy continued and which were allowed to deliver normally, there was no evidence of structural or physiological abnormalities in foetuses.

In vivo, the main metabolite of ulipristal acetate, the mono-N-demethylated (PGL4002) inhibited endometrial proliferation after oral administration with lower magnitude of efficacy than ulipristal acetate while di-N-demethylated (PGL4004) was only weakly active.

Safety pharmacology programme

Safety pharmacology studies have been conducted on the central nervous, cardiovascular and respiratory systems. Ulipristal acetate did not produce any unexpected or toxic effects in the safety pharmacology studies. The only effect of relevance is an increased arterial blood pressure observed in conscious female beagle dogs at 25 and 125 mg/kg, resulting in exposure margins of 36 and 337, respectively.

The studies are summarised in the table below.

Table 2. Summary of safety pharmacology studies performed with ulipristal acetate.

Organ System Evaluated Study Number	Species/ Strain Gender/ Number/ Group	Method of Administration	Doses Duration	Conclusions
CENTRAL NERVOUS SYSTEM				
Functional observation battery (Irwin test), **PGL-H-415**	Rat/SD 6F/group	po	5, 25, 125 mg/kg	Ulipristal acetate has no effect on behaviour or physiological changes.
CARDIOVASCULAR SYSTEM				
Action potential duration in Purkinje fibres, **PGL-H-412**	Dog/Beagle	*In vitro*	1, 3, 10 µM (0.475, 1.425, 4.75 µg/mL)	Ulipristal acetate is unlikely to have an effect on cardiac sodium channels.
HERG tail current, **PGL-H-413**	Transfected HEK293 cells	*In vitro*	10 µM (4.75 µg/mL)	Ulipristal acetate had no effect on HERG tail current.
Cardiovascular effects (arterial blood pressure, heart rate and ECG) in conscious, telemetered female beagle dogs **PGL-H-416**	Dog, Beagle 4 F/group	The animals were orally dosed sequentially with 7 days between doses of ulipristal acetate. Recordings were made for up to 24 hours after dosing.	5, 25, 125 mg/kg	Ulipristal acetate significantly increased blood pressure. The NOAEL was 5 mg/kg. The exposure margin at NOAEL is slightly below clinical exposure (348 ng*h/ml divided by 548 ng*h/ml). The exposure margin at 25 mg/kg is 14 times the clinical exposure.
RESPIRATORY SYSTEM				

Respiratory parameters (respiratory rate and tidal volume) **PGL-H-414**	Rat/SD 8F/group	Plethysmography chambers	5, 25, 125 mg/kg po	Ulipristal acetate had no effect on the respiratory parameters investigated.

Table 3. Safety margins of animal exposure in safety pharmacology studies performed with ulipristal acetate.

Species	Dose [a]	C_{max} µg/mL		Therapeutic ratio [d]		AUC_{0-24} h.µg/mL		Therapeutic ratio [d]	
		Ulipristal acetate	PGL 4002	Ulipristal acetate	PGL 4002	Ulipristal acetate	PGL 4002	Ulipristal acetate	PGL 4002
Rat	5 mg	0.681	1.375	11	63	3.645	3.876	17	46
	25 mg	3.418	1.562	53	71	29.779	11.064	137	130
	125 mg	8.908	3.684	139	167	72.407	25.443	334	299
Dog	5 mg	0.130	0.185	2	8	0.348	0.438	2	5
	25 mg	2.153	1.426	34	65	7.727	7.961	36	94
	125 mg	7.360	2.790	115	127	73.200	42.440	337	499
hERG assay / Purkinje fibres	10 µM / 4.64 µg/mL	4.750		74 [c]		-		-	

[a] Human dose (10mg/day) and animal dose (mg/kg); [b] Steady state exposures after 10 days of daily administration (PGL09-023); [c] Ratio calculated based on the total fraction in human plasma; [d] Therapeutic ratios were based on a clinical steady state exposure of 10 mg/day, since steady state data at 5 mg/day (the proposed clinical dose) was not readily available. Thus therapeutic ratios at a clinical dose of 5 mg/day are likely to be higher.

Pharmacodynamic drug interactions

A receptor binding study was submitted in order to investigate the affinity of ulipristal acetate to other than hormonal receptors. This study is summarised in the table below.

Table 4. Summary of a receptor screen performed *in vitro* with ulipristal acetate.

Type of Study, report	TEST SYSTEM	Test conditions	Comment
Receptor binding assay of ulipristal acetate and its metabolite PGL4002, **PGL-H-470**	78 receptors, ion channels and transporter systems	In vitro 10^{-5}M range	Significant binding of ulipristal acetate and PGL4002 at the glucocorticoid receptor. Ulipristal acetate also partially prevented binding of the cognate reference compounds to PPARγ and to a Cl- channel, whilst PGL4002 exhibited residual binding affinity for the cannabinoid receptor 1.

2.3.3. Pharmacokinetics

The pharmacokinetics of ulipristal acetate were determined in mice (CD-1), rats (Sprague Dawley), rabbits (New Zealand White), dogs (Beagle) and monkeys (Cynomolgus). Absorption, distribution, metabolism and excretion of ulipristal acetate were studied in rats and monkeys using oral and intravenous dosing. The pharmacokinetics of ulipristal acetate are summarized in the table below.

Table 5. Summary of pharmacokinetics for ulipristal acetate

Absorption	Rapidly and well absorbed after oral administration to mice, rats, rabbits,

	dogs and monkeys. C_{max} = 1 h in rats, 1-2 hours in dogs and 4 h in monkeys following oral administration.
Bioavailability	Rats approximately 80%. Monkeys approximately 112%. Human: No data
Dose proportionality	The exposure appeared to be less than proportional over the dose range 5 to 125 mg/kg for both ulipristal acetate and the metabolite PGL4002 in rats but the converse was seen in dogs. When analysed by RIA, exposure of rats and rabbits increased less than proportionally over the dose range 50-1250 mg/kg. Non-linear kinetics in humans, with less than dose proportional increase in exposure.
Terminal plasma half-life	Rat: 6 hrs following oral administration Monkey: 87 hrs following oral administration Human: 32 hours after oral administration
Distribution	Highly protein bound (96.7-99.5%) to plasma proteins of mouse, rat, rabbit, dog, monkey and human. ^{14}C-ulipristal acetate was widely distributed in rats and monkeys. Higher concentrations of radioactivity were seen in pigmented tissues (uveal tract, pigmented skin and meninges). No human data on excretion into milk. No information on distribution over placenta.
Metabolism	Rapid and extensive metabolism possibly via cytochrome P450 (CYP3A4). A large number of metabolites are produced, up to 28 in rat and 20 in monkeys. *In vivo* metabolism data in humans are very limited.
Excretion	Rats and monkey: main route via faeces (83.3-44.7%). Biliary excretion was observed in the rats.

Method of Analysis

Assays for ulipristal acetate have been developed based on radioimmunoassay (RIA) and LC-MS/MS techniques.

The RIA assay was used to support the initial pharmacokinetic studies and also the toxicokinetic analyses. The average limit of detection was 1±0.1 pg/tube. LC-MS/MS methods were developed to support the safety pharmacology studies in rat and dog and were shown to be specific for both ulipristal acetate and PGL4002, with a limit of quantification of 1 ng/mL for both analytes.

In addition to this, an LC-MS/MS assay for the ulipristal acetate and its metabolite PGL4002, in cynomolgus monkey plasma has been performed. The method is accurate and precise for the determination of PGL4001 and PGL4002 in the validated calibration range from 1.00 to 500 ng/mL (Study pgl09-003).

Absorption

The absorption of ulipristal acetate is rapid and complete with bioavailability of approximately 80% in the rat and 112% in the monkey. Cmax was obtained after 1 h in rats, after 1-2 hours in dogs and after 4 hours in monkeys. In the rat and rabbit, the exposure to ulipristal acetate increased less than proportional, while the opposite was observed for the dog.

Distribution

The distribution of radiolabeled (^{14}C) ulipristal acetate to tissues has been investigated in the albino rat and in the pigmented rats. Ulipristal acetate related radioactivity was widely distributed in the body, peak concentrations of radioactivity generally occurred 1 hour after dosing. Quantifiable radioactivity was still present in all tissues at the final sampling time of 3 days, indicating a fairly slow turnover of radioactivity/active substance. In support of the present application, a tissue distribution study with ^{14}C-ulipristal acetate in female pigmented rats has been performed. Following oral administration, radioactivity was absorbed and widely distributed, with peak concentrations occurring in most tissues 3 days after dosing which had declined by 7 days. Radioactivity was still visible after 28 days in most tissues. Levels of radioactivity in the uveal tract/retina (melanin containing tissue) were higher than in most other tissues, suggesting that ulipristal acetate-related material did bind to melanin. Since concentrations at 28 days were similar to those measured at 7 days, the binding was likely not reversible, and elimination from the uveal tract/retina is related to the turnover of melanin within the tissue. These findings could have been a concern. However, the earlier performed phototoxicity study was negative up to the limit of solubility for ulipristal acetate and therefore no concern remains.

In addition, a distribution study was also performed in the monkey with results only available from the final blood sampling 14 days after dosing. At this time, only liver and gall bladder had concentrations greater than 1 µg equiv/g, with lesser quantities in thyroid, kidney cortex, adrenal and spleen: at this time, mean levels in blood were 0.064 µg.equiv/g whilst the total radioactivity remaining in the animals accounted for 1.1-1.6% of the administered dose. Since, quantifiable radioactivity was still present in some tissues at the sampling time of 14 days; a slow turnover of radioactivity/active substance in monkey is indicated.

Ulipristal acetate is highly bound to plasma proteins in all animal species investigated including humans.

Metabolism

Ulipristal acetate is rapidly and extensively metabolised in rats and monkeys. The *in vitro* metabolism data in humans are quite limited, only CYP isoenzymes were tested, while *in vivo* data indicate presence of other pathways, e.g. acetylation. The *in vitro* studies showed formation of two metabolites, PGL4002 and PGL4004.

In vitro metabolism was studied in liver microsomes from female mouse, rat, rabbit, dog, monkey and human liver for 10 or 60 minutes and resulted in a metabolic turnover of 32-79% of ulipristal acetate after 60 minutes incubation in the presence of β-NADPH. In all species, the same two principal metabolites were produced, however, the identity of those were not reported in the study. Additionally, some minor metabolites were detected in the animal species which were not detected with human microsomes. *In vitro*, no metabolites were detected that were unique to humans. No significant metabolism was observed in the absence of β-NADPH, suggesting a role for cytochrome P450 in the metabolism of ulipristal acetate.

To conclude, the *in vivo* metabolism data in humans are limited and further information will be requested from the Applicant (see clinical Pharmacokinetic AR). Based on the limited amount of data available in animals, both rats and monkeys can be considered relevant animal species.

Excretion

Ulipristal acetate is mainly excreted via faeces in the rat and cynomolgus monkey following both oral and intravenous administration. Biliary excretion was identified as a major contributor in the rat.

Pharmacokinetic drug interactions

In vitro metabolism studies with human liver microsomes in the absence and presence of NADPH (PGL-H-429) implicated cytochrome P450 enzymes in the metabolism of ulipristal acetate and studies with supersomes showed cytochrome P450 to be the major isoenzyme involved (PGL-H-430).

Ulipristal acetate has the potential to inhibit CYP2D6 and CYP3A4, based on *in vitro* data (PGL-H-430). However, the metabolite PGL4002 (PGL09-010) was not shown to interact with the major CYP enzymes at clinically relevant concentrations.

Ulipristal acetate and PGL4002 did not demonstrate an induction effect on CYP1A2 or CYP3A4 activity at any of the tested concentrations for each donor in the induction study (PGL09-008). Ulipristal acetate appears to be a potent P-gp inhibitor *in vitro* in Caco-2 cells (PGL09-007) with an IC_{50} value of 0.73 µM (0.34 µg/ml). The inhibitory effect was in a similar range as for ketoconazole and cyclosporine at high concentrations.

2.3.4. Toxicology

Ulipristal acetate has been evaluated for its toxicity in rats and monkeys dosed daily for up to 6 and 9 months, respectively. In addition, reproductive and developmental toxicity studies in rats and rabbits, *in vitro* and *in vivo* genotoxicity assays as well as a phototoxicity study was carried out.

Single dose toxicity

Single dose toxicity studies with ulipristal acetate have been conducted in rats and rabbits using the oral route of administration. The table below provides an overview of the single dose toxicity studies submitted for Ulipristal acetate.

Table 6. Overview of the single dose toxicity studies performed with ulipristal acetate.

Study ID / GLP	Species / Sex / Number / Group	Dose / Route mg / kg	Approx. lethal dose / observed max non-lethal dose	Major findings
PGL-H-431	Rat/SD/10F/group	0, 1250/po	<1250	Mortality: One treated rat was found moribund on day 2 and euthanized (clinical signs see below + apnea, ptosis, lethargy, tremors and convulsions on day 1). Clinical signs: No effect on body weight. Decreased faecal output on day 1 and in some animals also on days 2-3, discharge from the eyes or nose (6/10), piloerection (2/10) and decreased motor activity (1/10). Liver and kidney weights were increased, ovary weight decreased.
PGL-H-432	Rabbit/NZW/10F/group	0, 1250/po	>1250	Mortality: Two animals died, the deaths were by the assessor not considered related to treatment.

				Clinical signs: Food intake and faecal output were reduced for 4 to 6 days after dosing. No effect on organ weights and no histopathological changes.

F = female/s, M = male/s

Repeat dose toxicity

Pivotal repeated-dose toxicity studies were conducted for 6-month in rats and cynomolgus monkeys, supported by 14-day preliminary studies. Furthermore, a 9-month toxicity study was conducted in cynomolgus monkeys followed by a recovery period of 2 months.

Administration of ulipristal acetate (1, 5 and 25 mg/kg/day) to rats in the 6-month toxicity study caused changes in haematological (increased white cell, lymphocyte and neutrophils; reduced erythrocyte numbers, haematocrit and haemoglobin) and biochemical (reduced sodium, chloride; increased globulin, total protein and cholesterol) parameters. Organ weight analysis showed increased liver and adrenal weights and decreased ovaries, uterus and thyroid weights at the 5 and 25 mg/kg/day dose levels. On histological examination, these correlated with adrenal cortical and liver hepatocyte hypertrophy, ovarian follicular cysts and follicular atresia and uterine glandular dilation: pituitary hyperplasia and mammary galactoceles were also noted. These histological changes were most notable in animals treated with 5 or 25 mg/kg/day but the changes in mammary glands and ovaries were also seen at 1 mg/kg/day. There was a significant positive correlation between pituitary weights and serum prolactin levels and between adrenal weights and serum corticosterone levels. Treatment-related changes were seen at all dose levels and it was not possible to determine a NOEL in this study.

The 6-month study in cynomolgus monkeys was conducted at dose levels of 1, 5 and 25 mg/kg/day. Administration of ulipristal acetate disrupted the hypothalamic-pituitary-adrenal axis with increased cortisol and prolactin levels. Although hormone levels were altered at all dose levels, the consequences were most apparent at the 5 and 25 mg/kg/day dose levels. The menstrual cycle was disrupted in mid- and high-dose animals with some high-dose animals being acyclic throughout the study. Lymphocyte numbers were reduced and neutrophil numbers increased at these dose levels. Adrenal weights were increased in high-dose animals (there was a significant correlation between adrenal weights and serum cortisol levels), consistent with the hypertrophy observed at histology; although thymus weights were decreased at this dose level, there were no histological correlates. Histology also showed cystic dilatation of uterine endometrial glands in mid- and high-dose animals, with one high-dose animal showing mild squamous metaplasia.

The 14-day study in rats showed several changes in terms of laboratory parameters, organ weights and histopathology. These changes were mainly confined to the mid- and high-dose levels of 20 and 100 mg/kg/day with effects on ovaries and uterus in only a few animals at the low dose (4 mg/kg/day), which was the NOEL in this study.

The 14-day study in rhesus monkeys had only two dose levels, 20 and 100 mg/kg/day. Two animals in the high-dose group were particularly affected by treatment with one animal euthanized on day 8. No treatment-related changes in haematology parameters were observed while high-dose animals showed changes in some biochemistry parameters which are considered of low clinical relevance. Serum cortisol levels showed a general trend of increasing values in the high-dose group. Organ weights were increased in the high-dose group for liver, thyroid and heart and, for animals in both treated groups, in the spleen, adrenals, ovaries and kidneys. A dose related increase in mucous cells in the cervix in low-

and high-dose groups and a decreased bone marrow cellularity in two high-dose animals were observed at histopathology.

The 9-month toxicity study in female cynomolgus monkeys was performed with identical dose-levels as in the previous 6-month study, 1, 5 and 25 mg/kg/day. Two female in the control group and two in the 25 mg/kg/day group were allowed to recover for 2 months. In general, similar signs as observed in the previous 6-month study were noted; interruptions of the menstrual cycle, increased levels of total leukocytes and neutrophils, increased prolactin and serum cortisol levels all observed at 5 and 25 mg/kg/day. Dose-dependent histopathological findings consisted of cystic endometrial hyperplasia and/or squamous metaplasia of the uterine endometrial epithelium and oviduct findings. Cystic endometrial hyperplasia was characterized by cystic dilatation of the endometrial glands and increased number of the glands, accompanied by thickening and proliferation of the endometrial mucosa. This finding was seen in conjunction with squamous metaplasia of the epithelium. At recovery, findings were limited to few localized cystic dilations of the endometrial glands and some hyperplastic piling of the localized uterine mucosa. Furthermore, changes in the oviducs were observed; dilation of the central oviduct lumen and discrete cyst formation in the mucosal epithelium of the oviduct wall. One animal had a finding of squamous metaplasia of the oviduct mucosa, similar to that seen in the uterus. At recovery, no macroscopic findings were noted in one animal and in the other animal microscopic findings of minimal or mild severity were observed.

Genotoxicity

The genotoxicity of ulipristal acetate has been studied with respect to gene mutations in bacteria, chromosomal aberrations *in vitro* in human lymphocytes, mutations in TK locus *in vitro* in Mouse Lymphoma L5178Y cells and *in vivo* in the mouse micronucleus test in bone marrow. No genotoxic potential was evident in any of the test systems when tested up to appropriate concentrations and dose levels according to guidelines.

Carcinogenicity

No carcinogenicity studies with ulipristal acetate have been submitted.

Reproduction Toxicity

A standard package of reproductive toxicity studies have been conducted with focus on embryofoetal development and possible effects on pups from dams which were dosed during the early days of pregnancy, of relevance for the proposed indication. Doses in these studies were low so as to provide data at levels which did not impair pregnancy.

An embryofetal developmental study was conducted in the rat with ulipristal acetate 0, 0.1 0.3 and 1 mg/kg. At 1 mg/kg the pregnancy rate was reduced to 84% and a significant increase in post-implantation loss was observed. 9 out of 21 pregnant females had uterine implantations comprised entirely of resorption sites. Of dams that had viable foetuses, a decrease in the number of live fetuses per female was noted. No adverse effects were noted in a male rat fertility study when the animals were dosed p.o. with ulipristal acetate 10 mg/kg. There was no evidence of a teratogenic effect of ulipristal acetate in this rat study.

Female rabbits were dosed with ulipristal acetate 0, 0.1 0.3 and 1 mg/kg and the pregnancy rate was reduced at the high dose level. Further, similar results as seen in rats were noted also in rabbits and a NOEL for developmental toxicity was established at 0.3 mg/kg both in the rat and rabbit.

Pregnant rats were treated with ulipristal acetate 0.5 and 1 mg/kg during gestation day 0 to 3 in order to mimic an potential exposure of a human embryo shortly after the unprotected intercourse. At both dose levels the gestational length was increased and at 1 mg/kg the number of pregnant animals was reduced. No adverse effects were seen on development of the F1 generation including reproductive capacity. In the *in vivo* primary pharmacodynamic study performed in cynomolgus monkeys referred to in section II.1, no evidence of structural or physiological abnormalities in fetuses or infants that survived exposure to ulipristal acetate (0.5 and 5 mg/kg po) at gestation days 23-26 were seen. The data comprised 4 and 2 live births from dams dosed orally with 0.5 and 5.0 mg/kg/day, respectively, and one live birth from a dam treated intramuscularly with 0.5 mg/kg/day.

Pregnant rats were treated with high doses of ulipristal acetate 2, 4 or 8 mg/kg during late (Day 17-19) gestational phase. Ulipristal acetate induced premature parturition in all animals irrespective of dose and all pups delivered were found dead in their placental membrane.

Toxicokinetic data

The toxicokinetics of ulipristal acetate were characterized in rats and monkeys. Only female animals were used in the toxicological investigation.

In rats, the increase in exposure to ulipristal acetate and PGL4002 using LC-MS/MS was sub-proportional in the dose range of 5 to 125 mg/kg/day together with an increase of the metabolic ratio ulipristal acetate/PGL4002 suggesting that the metabolism of ulipristal acetate was saturated with increasing doses (PGL-H-421). Similar changes in exposure were obtained by RIA measurement after 6 months of repeated oral dosing (PGL-H-435). In pregnant rats, the increase in systemic exposure for ulipristal acetate and PGL4002 using LC-MS/MS was slightly less than dose- proportional between 0.1 and 0.3 mg/kg/day for C_{max}, and dose- or supra-proportional for AUC_{0-6h}, with, in all cases, the systemic exposure of ulipristal acetate being higher than that of PGL4002 (PGL-H-471).

In monkeys, toxicokinetic data showed a general pattern of dose- or supra-proportional increase in ulipristal acetate and PGL4002 exposure (C_{4h} and $AUC_{1-270\ days}$) using LC-MS/MS with increasing dose level (1 to 25 mg/kg/day) following oral administration over 9 months; similar findings were seen from 6 month dosing using RIA measurement (PGL-H-436; PGL09-001). Multiple sampling time points in the 9 month monkey study showed low exposure at 1 mg/kg/day throughout the study. However, steady state was quickly established at higher dose levels with consistent values seen throughout the dosing period for both parent drug and PGL4002 (PGL09-001). Furthermore, concentrations of ulipristal acetate were less than those of PGL4002 at 1 and 5 mg/kg/day, and approximately equal to those of PGL4002 at 25 mg/kg/day.

Local Tolerance

No local tolerance studies were submitted.

Other toxicity studies

Photosafety

An evaluation of the *in vitro* phototoxicity of ulipristal acetate (2.5-30 µg/mL) on Balb/c 3T3 fibroblasts using the neutral red uptake assay has been performed (study PGL-H-448). The highest concentration of ulipristal acetate used was limited by solubility. When tested up to the limit of solubility, ulipristal acetate was not phototoxic.

2.3.5. Ecotoxicity / environmental risk assessment

Based on the CHMP Guideline on the Environmental Risk Assessment of Medicinal products for Human Use (EMEA/CHMP/SWP/4447/00, 01 June 2006), an action limit is in principle not applicable for ulipristal acetate, as it is a selective progesterone receptor modulator and a potential endocrine disruptor. Based on the extensive metabolism and very limited excretion of unchanged ulipristal, its therapeutic use is unlikely to represent a risk to the environment. However, a Phase II environmental risk assessment is recommended, and underway, to further characterize the potential endocrine modulating properties of ulipristal acetate in the environment.

Table 7 Summary of main study results

Substance (INN / Invented Name): ulipristal					
CAS-number (if available):					
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
$PEC_{surfacewater}$, refined	<0.01	µg/L			Not applicable
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 106				To be provided
Ready Biodegradability Test	OECD 301				To be provided
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD 201	NOEC		µg/L	To be provided
Daphnia sp. Reproduction Test	OECD 211	NOEC		µg/L	To be provided
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	NOEC		µg/L	Full fish life cycle to be provided.
Activated Sludge, Respiration Inhibition Test	OECD 209	EC		µg/L	To be provided
Phase IIb Studies					
Fish Bioaccumulation	OECD 305	BCF		L/kg	To be provided

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

- a phase II ERA for ulipristal acetate.

2.3.6. Discussion on non-clinical aspects

The non-clinical data submitted reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, and genotoxicity. Most findings in general toxicity studies were related to its action on progesterone receptors (and at higher concentrations on glucocorticoid receptors), with antiprogesterone activity observed at exposures similar to therapeutic levels.

Based on the CHMP Guideline on the Environmental Risk Assessment of Medicinal products for Human Use (EMEA/CHMP/SWP/4447/00, 01 June 2006), an action limit is in principle not applicable for ulipristal acetate, as it is a selective progesterone receptor modulator and a potential endocrine disruptor.Based on the extensive metabolism and very limited excretion of unchanged ulipristal acetate, its therapeutic use is considered unlikely to represent a risk to the environment. A phase II ERA has been recommended post approval and is currently ongoing to gather further information about the fate and effects of the drug substance as a potential endocrine modulator in the environment.

Due to its mechanism of action, ulipristal acetate has an embryolethal effect in rats, rabbits (at repeated doses above 1 mg/kg), guinea pigs and in monkeys. The safety for a human embryo is unknown. At doses which were low enough to maintain gestation in the animal species, no teratogenic potential was observed. Reproduction studies performed in rats at doses giving exposure in the same range as the human dose have revealed no evidence of impaired fertility due to ulipristal acetate in treated animals or the offspring of treated females. As ulipristal acetate is administered orally, no specific local tolerance studies were conducted. No signs of irritation of the gastrointestinal tract were observed in toxicology studies.

Based on the non-clinical dossier, the following amendments have been made to the Product Information:

Section 4.3 of the SmPC has been amended to include the following contraindications: hypersensitivity to the active substance or to any of the excipients, pregnancy, breastfeeding, genital bleeding of unknown aetiology or for reasons other than uterine fibroids, uterine, cervical, ovarian or breast cancer and treatment beyond 3 months.

Section 4.4 of the SmPC includes warnings and precautions on contraception. Esmya should only be prescribed after careful diagnosis. Pregnancy should be precluded prior to treatment. Concomitant use of progestagen-only pills, a progestagen-releasing intrauterine device or combined oral contraceptive pills is not recommended. Although a majority of women taking a therapeutic dose of Esmya have anovulation, a non hormonal contraceptive method is recommended during treatment.

This section also includes a precaution for use with concomitant treatments. Ulipristal acetate is not recommended for patients receiving P-glycoprotein (P-gp) substrates (e.g. dabigatran etexilate, digoxin). Co-administration of moderate or potent CYP3A4 inhibitors and ulipristal acetate is not recommended. When prescribing ulipristal acetate to patients receiving CYP3A4 inducers, plasma levels of ulipristal acetate may be reduced. Concomitant use of ulipristal acetate and potent CYP3A4 inducers (e.g. rifampicin, carbamazepine, phenytoin, St John´s wort) is not recommended.

Section 4.5 of the SmPC identifies potential interactions between Ulipristal acetate and other medicinal products. Medicinal products which could affect ulipristal acetate are hormonal contraceptives, CYP3A4 inhibitors, and CYP3A4 inducers. Ulipristal acetate could interfere with the action of hormonal contraceptives and P-gp substrates.

The basis for the assessment of long term safety of ulipristal acetate has been a 9-month toxicity study in cynomolgus monkeys with a 2 month recovery period. In this study, histological changes resembling progesterone receptor modulator associated endometrial changes were noted at doses from 1 mg/kg/day. This has been a concern but is considered acceptable given that the proposed indication for Esmya with maximum duration of treatment set to 3 months.

No carcinogenicity studies with ulipristal acetate have been performed given the short treatment duration (a maximum of 3 months). However, cystic hyperplasia of the uterine endometrium was observed at low exposure during the 9 month repeat dose toxicity study in monkeys, which is of concern.

To address the absence of carcinogenicity studies, the applicant has initiated as part of the RMP a 104-week carcinogenicity study in rats and a 26-week carcinogenicity study in transgenic TgRasH2 mice. It is considered acceptable for these studies to be performed post-approval, as no signs of malignant changes were noted in the endometrial data collected up to 38 weeks after three month treatment with ulipristal in the clinical studies.

Two non-clinical carcinogenicity studies are also ongoing to determine the potential of ulipristal acetate for neoplasia (PGL09-005 and -PGL10-005). In addition to this, the findings in cynomolgus monkeys

observed in the repeat dose toxicity study have been adequately described in the section 5.3 of the SmPC.

2.3.7. Conclusion on the non-clinical aspects

The non-clinical data for Esmya are adequate to support the market authorisation. The applicant has initiated and will submit the results of a 104-week carcinogenicity study in rats and a 26-week carcinogenicity study in transgenic TgRasH2 mice as a post-authorisation measure to determine the potential of ulipristal acetate for neoplasia. These post-authorisation measures are adequately covered in the RMP.

2.4. Clinical aspects

2.4.1. Introduction

GCP

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

The clinical studies were performed in accordance with the Declaration of Helsinki, the ICH Harmonized Tripartite Guideline for GCP, the European Union Clinical Trial Directive and all applicable local regulatory requirements.The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC .

- Tabular overview of clinical studies

The following table summarizes all the clinical studies submitted.

Table 8. Summary of ulipristal acetate clinical study programme

Summary of ulipristal acetate clinical development (safety populations)

Phase	Study	Double-blind	Ulipristal acetate doses (mg) N									Control (n)	Planned Treatment Duration
			1	2.5	5	10	20	30	50	100	200		
Pivotal Phase III studies in target population													
III	PGL07-021	Yes			95	98						Placebo (48)	12 Weeks[a]
III	PGL07-022	Yes			97	103						GnRH-agonist[b] (101)	12 Weeks[a]
Repeated-dose studies in target population													
II	PGL-N-0287	Yes				8	6					Placebo (8)	12 Weeks
II	PGL-N-0090	Yes				16[c]	16[c]					Placebo (13)	12 Weeks[c]
III	PGL09-026	No				124[g]						NA	12 Weeks[g]
Repeated-dose studies in healthy subjects													
II	PGL-H-510	Yes		12	12	11						Placebo (11)	3 months
I	PGL09-023	Yes				8	8		8			Placebo (8)	10 days
Single-dose studies in healthy subjects													
I	PGL-H-503	No	6			6			6	7	6	Placebo (5)	Single-dose
I	PGL09-004	No			33	33						-	
I	PGL-H-501	No				10						-	
I	PGL-H-505	Yes				11			11	10		Placebo (12)	
I	PGL-H-506	No				13[d]			14[d]	14[d]		Placebo (15[d])	
I	PGL09-022	No					18					Erythromycin interaction	
I	PGL09-015	No					5					-	
I	PGL-H-504	No						20				-	
I	PGL-H-512	No						19				-	
I	PGL-H-516	No						53				-	
II	PGL-H-511	Yes						35				Placebo (35[e])	
I	PGL11-002	No				18						NA	
Single-dose studies in subjects requiring emergency contraception													
II	PGL-H-508	Yes				613			413			-	Single-dose
III	PGL-H-509	No						1533				-	
III	PGL-H-513	Single-blind[f]						1104				Levonorgestrel 1.5 mg (1117)	
II	PGL-H-507	Yes							832			Levonorgestrel 0.75 mg (840)	

Shaded studies are those included in the HRA Pharma application for ulipristal acetate use as an emergency contraceptive (Ellaone®, EPAR. EMEA/261787/2009)

As studies were carried out by various sponsors, all studies have been given a new number according to PregLem's classification system (see Section 2.2 for original study numbers).

a Extension periods consisting of safety follow-up visits at Weeks 26 and 38 were also carried out; see PGL07-021 and PGL07-022 Part B CSRs included in Module 5.

b Leuprorelin 3.75 mg once monthly injections.

c At the end of the first 12 weeks, all subjects were given the option to take ulipristal acetate (unblinded) for the following 12 weeks. Each group included 2 subjects randomized to placebo for the first 3 months who received ulipristal acetate in the 3 month extension period. Three subjects in the ulipristal acetate 5 mg/day group and 6 subjects in the ulipristal acetate 10 mg/day group continued into the 3 month extension period.

d Data comes from a published article (18). In total 61 subjects received study treatment in this study but in the publication, group numbers are only given for 56 subjects included in analyses.

e The same 35 subjects received ulipristal acetate and placebo in this crossover design study.

f Sponsor and Subjects were blinded, Investigator unblinded.

g Interim data available (cut-off date 15 March 2011)

2.4.2. Pharmacokinetics

Absorption

The active substance ulipristal acetate is a weak base with pH dependent and poor aqueous solubility (Study PGL10-12). Micronization increases the bioavailability and micronized drug substance is used in the 5mg tabled formulation. The absolute oral bioavailability of ulipristal acetate has not been determined.

The bidirectional permeability of ulipristal acetate and the metabolite PGL4002 was assessed using human Caco-2 cell monolayers (PGL09-007). Some problems with non-specific binding of the test compounds to the experimental devices were encountered in this study, which makes the results from this experiment inconclusive. It can therefore not be immediately concluded that ulipristal acetate is a high-permeability substance. Ulipristal acetate and PGL4002 do not appear to be P-gp substrates. It was not investigated whether ulipristal acetate is a substrate (or inhibitor) of other transporters, e.g. uptake or efflux (biliary) transporters in the liver.

Bioequivalence

The ulipristal acetate formulation used in the pivotal phase III studies is a tablet formulation containing 5 mg ulipristal acetate. Thus, the BE studies submitted (PGL09-004, PGL-H-504, PGL-H-501, PGL-H-516) provide information on the impact of the formulation on bioavailability but are not crucial to bridge data between formulations.

In the bioequivalence study (PGL09-004) comparing 2 different ulipristal acetate tablet formulations, a small deviation from strict bioequivalence was shown for C_{max} for the parent drug ulipristal acetate for both the 5 and 10 mg strengths. The deviation was small and not likely relevant and furthermore, the phase III studies were conducted with the final formulation to be marketed.

Study PGL-H-504 was a single dose, non-comparative study of a 30 mg ulipristal acetate tablet formulation. The study was submitted as part of the PK profile characterization.

Study PGL-H-516 was a two-treatment, single-dose, crossover study in healthy female volunteers comparing the bioavailability of ulipristal acetate for a 30 mg tablet manufactured at two different sites. Bioequivalence was demonstrated between the tablets studied.

No issues related to bioequivalence between different formulations have been identified.

Food interaction

The food interaction study (PGL-H-512) was conducted with a ulipristal acetate 30 mg tablet and had an adequate design. No dramatic effect of food on the exposure of ulipristal acetate and its active metabolite was found, although the PK profile was changed to some extent. AUC was increased 26% on average, median tmax increased from 0.75 hours to 3.0 hours and Cmax showed a mean decrease of 44%. No study has been conducted with the 5 mg Esmya tablet in the dossier.

Interaction with medicinal products affecting gastric pH

An *in vivo* interaction study (PGL11-002) was submitted in which the effect of repeated dosing of esomeprazole on the pharmacokinetics of ulipristal acetate (5mg) was studied. Administration of ulipristal acetate (10 mg tablet) together with the proton pump inhibitor esomeprazole (20 mg daily for 6 days) resulted in approximately 65% lower mean Cmax, a delayed tmax (from a median of 0.75 hours to 1.0 hours) and 13% higher mean AUC. This effect of medicinal products that increase gastric pH is not expected to be of clinical relevance for daily administration of ulipristal acetate tablets.

Distribution

Ulipristal acetate has a high degree of binding to plasma proteins (98%) and to blood cells, resulting in a free fraction of about 1% (PGL-H-427, PGL-H-428, PGL09-011). The protein binding of the active metabolite PGL4002 was somewhat lower compared with that of ulipristal acetate (96-97%). There is no information about the volume of distribution of ulipristal acetate due to the lack of intravenous pharmacokinetic data. Ulipristal acetate may be distributed in milk.

Metabolism

The *in vitro* metabolism data are limited and only microsome studies has been submitted (PGL-H-429, PGL-H-430) but not studies using hepatocytes. Furthermore, only CYP isoenzymes were tested, while *in vivo* data indicate presence of other pathways, e.g. acetylation. The *in vitro* studies showed formation of two metabolites, PGL4002 and PGL4004. CYP3A4 seemed to be involved in the formation of these metabolites. An *in vivo* interaction study with the CYP3A4 inhibitor erythromycin, showed an approximately 3-fold increase in the exposure to ulipristal acetate, thus, providing support for involvement of CYP3A4 in the *in vivo* metabolism.

In vivo metabolism data are available from a mass balance study (PGL09-015). In plasma, complete identification of the radioactivity in plasma in the 1 hour-sample was achieved. However, a later time points no metabolite profiling seems to have been performed. Throughout the dossier, the applicant is mainly focused on PGL4002 as being the major metabolite, however, considering the overall metabolism pattern and mass balance data this may be a relatively small pathway. PGL4002 probably contributes to some extent to the activity of ulipristal acetate, with plasma levels that are about 30% of those of the parent drug, a somewhat lower protein binding and a potency similar to ulipristal acetate.

Incomplete information is also available on the metabolite pattern in faeces and urine.

An *in vitro* study has been conducted to assess the involvement of P-gp in the absorption of ulipristal acetate. However, no studies have been conducted to investigate *in vitro* whether other transporter proteins (efflux/uptake) are involved in the absorption, distribution or elimination of ulipristal acetate.

The consequences of genetic polymorphism have not been studied. Known polymorphic cytochrome P450 isoenzymes, e.g. CYP2D6 or CYP2C19 do not seem to be involved in the ulipristal metabolism, based on *in vitro* data. Acetylation seems to be one metabolic pathway for ulipristal acetate and N-acetyl transferase is known to be polymorphic. The importance of this pathway is, however, unknown.

Elimination

A mass balance study with radio-labelled ulipristal acetate has been submitted (PGL09-015). An oral solution containing ^{14}C-ulipristal acetate was administered to 5 women at a dose of 20 mg. In plasma, the mean half-life of total radioactivity was much longer compared with the mean half-life of unchanged ulipristal acetate (120 vs. 51 hours). Based on $AUC_{0-\infty}$, ulipristal acetate and the metabolite considered to be the primary metabolite (PGL4002) together only constitute approximately 8% of the $AUC_{0-\infty}$ of total radioactivity.

Despite a prolonged sampling period (up to 264 hours post-dose), the overall mean recovery of radioactivity in excreta did not sum up to more than approximately 79%. The excretion was mainly faecal, with a mean of 72%. Some individuals showed a very late excretion of radioactivity in faeces.

Given that most subjects had a low faecal excretion during the first 48 hours after dosing and given the relatively fast absorption, the radioactivity in faeces indicates excretion of unchanged drug or metabolites, not of unabsorbed drug. In metabolite profiling attempts of faecal samples, no unchanged ulipristal acetate has been detected. The urinary excretion of radioactive material was low, with a mean of 6%.

Dose proportionality and time dependencies

Data on dose proportionality for ulipristal acetate has been submitted for doses across the range of 1 mg to 200 mg. Study PGL-H-503 covered a dose range of 1-200 mg in healthy pre-menopausal women in fasted state, with ulipristal acetate. In study PGL09-004, 5mg and 10mg doses were studied, and were shown to be proportional. In study PGL09-023, where the 10mg, 20mg and 50mg doses were studied, the exposure to ulipristal acetate increased somewhat more than dose proportional both after single and multiple dosing, however, the deviation from dose proportionality was not very large.

Study PGL09-023 provides the main source to multiple dose PK data for ulipristal acetate, although the therapeutic dose 5 mg/day was not studied. This study showed that with once daily administration, steady state is reached after 8-10 days, or possibly somewhat earlier. A comparison of single and multiple dose exposure data indicated no unexpected findings over time, neither unexpected accumulation nor signs of decreased exposure with time.

The inter-individual variability in exposure to ulipristal acetate is moderate to high (approximately 50%). There was no information about intra-individual variability.

Special populations

No studies in special populations have been submitted. The effect of renal impairment or hepatic impairment on the pharmacokinetics of ulipristal acetate has not been investigated. No population pharmacokinetic analysis has been performed as an alternative to specific pharmacokinetic studies.

Pharmacokinetic interaction studies

One *in vivo* interaction study (PGL09-022) was submitted in which the effect of repeated dosing of erythromycin on the pharmacokinetics of ulipristal acetate was studied. A small increase in C_{max} (18%) of ulipristal acetate was observed upon co-administration with erythromycin while the AUC values were approximately 3-fold higher with erythromycin. The mean half-life was not affected. The data suggests an effect on the gut CYP3A4 metabolism of ulipristal acetate, although a larger effect on C_{max} might have been expected if the inhibition was mainly pre-systemic. For the metabolite PGL4002, C_{max} was reduced by erythromycin co-administration to about 50% of the value without erythromycin. The AUC values were increased by approximately 50% and the mean half-life was doubled.

Pharmacokinetics using human biomaterials

No pharmacokinetic studies using human biomaterials were submitted.

2.4.3. Pharmacodynamics

Mechanism of action

Effects on progesterone action in target tissues

Progesterone receptor action of ulipristal acetate was demonstrated in vitro (Study PGL-H-410; Study PGL-H-411) evaluating the effects of ulipristal acetate on proliferative activity and apoptosis in cultured

human uterine leiomyoma cells. The results suggest that ulipristal acetate inhibits the proliferation of cultured leiomyoma cells by down-regulating proliferating cell nuclear antigen (PCNA) expression, and induces apoptosis by up-regulating cleaved caspase-3 and poly ADP ribose polymerase (PARP) expression and down regulating B-cell lymphoma 2 (Bcl-2) expression (see non-clinical section).

Effects on ovarian function after single doses of ulipristal acetate

Studies in regularly menstruating healthy women using single doses from 1mg to 200mg were submitted in order to demonstrate effects on ovarian function.

In Study PGL-H-505, patients were randomized to a single dose of 10, 50 or 100 mg of ulipristal or placebo in the mid-follicular phase of the menstrual cycle. The treatment cycle had been preceded by and was followed by a control cycle. Mid-follicular phase administration appeared to stun the follicle and delay ovulation in all active dose groups. All women on 50 or 100mg ovulated >1 week after treatment, whereas most of those receiving placebo or the 10mg dose ovulated within 1 week of treatment. Endometrial biopsies were obtained 5-7 days after ovulation and, compared with placebo, there was a delay in endometrial maturation at all doses of ulipristal.

In order to study effects of early luteal phase administration of Ulipristal (Study PGL-H-506), regularly menstruating women were randomized to receive a single dose of ulipristal: 10mg, 50mg or 100 mg or placebo given after ovulation and within two days of the LH surge. Four to six days after treatment, a transvaginal ultrasound was done to measure endometrial thickness and any ovarian cysts, if present, and an endometrial biopsy was obtained. The women were studied during a control, a treatment, and a post-treatment cycle. There was no significant difference among the treatment groups in the length of the follicular or luteal phase, or overall cycle length during the baseline, treatment or post-treatment menstrual cycles. Early luteal administration of 50 or 100 mg appeared to delay endometrial maturation and to decrease endometrial thickness without affecting luteolysis or menstrual cycle length.

The effect of ulipristal acetate on the length of the menstrual cycle was studied in PGL-H-504. Healthy women with normal menstrual cycle lengths were studied during a control, a treatment, and a post-treatment cycle. The women received a single dose of ulipristal: 1mg, 10mg, 50mg, 100 mg, 200 mg or placebo administered in the mid-luteal phase. When Ulipristal acetate was administered in the mid-luteal phase, no significant effect on menstrual cycle length was observed at doses up to 100 mg. However, subjects receiving a single 200 mg dose all had a shortened luteal phase and early menses.

In order to study the effect of a single oral dose of 30mg ulipristal acetate on the outcome of the leading follicle and more specifically to assess inhibition of follicular rupture, healthy regularly menstruating women were randomized in a cross-over design to a single oral dose of 30 mg ulipristal acetate or to placebo to be administered in cycles 1 and 4 when the lead follicle diameter had reached ≥18mm (Study PGL-H-511). Ulipristal acetate delayed or inhibited follicular rupture significantly compared to placebo even when administered immediately before ovulation (when LH surge has already begun).

Effects on ovarian function and endometrium during continuous daily administration of ulipristal acetate

The pharmacodynamic properties with regard to the hypothalamic-pituitary axis and the effects on the endometrium of continuous administration of ulipristal acetate were studied in healthy, regularly menstruating volunteers (Study PGL-H-510). After a control cycle, women were randomized to receive 2.5 mg/day, 5 mg/day, 10 mg/day or placebo throughout 3 months after which a post-treatment cycle followed.

Inhibition of ovulation, as defined by progesterone levels <3 ng/ml throughout the third treatment cycle, was seen in the majority of volunteers on 5mg and 10mg. No statistically significant impairment of follicular growth vs placebo was observed. Estradiol levels remained in the physiological range during the follicular phase in all groups, with FSH levels in the range of low normal values for the 5 and 10 mg/dose group as well as for anovulatory subjects in the 2.5 mg group. The LH surge was blunted but not down-regulated and remained in a range compatible with folliculogenesis.

The endometrial histology produced results indicating predominantly secretory endometrium in the treatment groups, despite suppressed circulating endogenous progesterone levels, which suggested a progesterone agonist effect of the compound. Bleeding days decreased with successive months of treatment, with amenorrhea achieved in 9/11 and 9/10 in the 5 and 10 mg groups, respectively, at month 3**.**

Primary and Secondary pharmacology

Four pharmacodynamic dose-response studies with 30mg ulipristal acetate formulation were submitted. However, no new pharmacodynamic studies have been submitted in relation to the proposed indication “treatment of uterine fibroids”.

Three studies involved a single-dose administration (PGL-H-503, PGL-H-505 and PGL-H-506). Only one study (PGL-H-510) is a repeated-dose study in which subjects received daily a single dose of ulipristal acetate (2.5 mg, 5 mg or 10 mg) over 12 weeks to study the minimal effective dose in ovulation inhibition. This pharmacodynamic study is consequently the most relevant.

Primary pharmacology

In the Phase II study (PGL-H-510) in healthy subjects, a dose-dependent effect was seen on amenorrhea and the anovulation rate. The majority of the subjects in the 5 and 10 mg/day group had amenorrhea and anovulation, whereas this was not the case for the 2.5 mg/day and placebo group. The percentage of amenorrhea and anovulation rate was comparable between the 5 and 10 mg/day group. Comparison of mean hormone levels for all treatment groups versus placebo did not show any statistically significant differences (FSH, LH, estradiol, cortisol, prolactin and testosterone), except for progesterone levels, which were in the majority of the subjects in the 5 and 10 mg/day group below 3 ng/ml throughout treatment cycle 3. Further, LH surge was blunted in 18.2%, 54.5% and 80% in the 2.5, 5 and 10 mg/day group, respectively.

There was no significant difference between treatment groups in terms of endometrial thickness. The histological patterns of normal cyclic endometrium were only displayed by a minority of subjects in the 5 (18%) and 10 (0%) mg/day group compared to placebo (55%) and the 2.5 (27%) mg/day group. Most subjects (64%) exhibited cystic dilated glands in the 5 mg group, whereas this was 0% in placebo, 9.1% (1 out of 11 subjects) in the 2.5 mg group and 10.0% (1 out of 10 subjects) in the 10 mg group. No specific patterns such as disordered architecture or abnormal vessels were present. There were no signs of endometrial hyperplasia or cellular atypia in any of the patients studied.

Secondary pharmacology

Ulipristal acetate reduces oestrogen concentrations by inhibiting ovulation via effects on follicle-stimulating hormone (FSH) and luteinising hormone (LH). Pre-clinical studies indicate that ulipristal acetate binds to the glucocorticoid and androgen receptors. The *in vivo* anti-glucocorticoid and anti-

androgen activity was demonstrated at doses approximately 50-fold greater than those needed for anti-progesterone effect.

Relationship between plasma concentration and effect

Trough levels of ulipristal acetate and PGL4002 were determined at weeks 5, 9 and 13 (PGL07-021, PGL07-022). No correlation was observed between ulipristal acetate and/or PGL4002 mean trough concentrations and other end-points, such as endometrium thickness, total myoma volume, uterine volume

Pharmacodynamic interactions with other medicinal products or substances

No specific pharmacodynamic interaction studies have been submitted.

2.4.4. Discussion on clinical pharmacology

Esmya is intended for use in fertile women and the population included in the pharmacokinetic studies (healthy female volunteers between 18 to 50 years) is therefore deemed adequate. No population pharmacokinetic analyses or studies in special populations have been performed. Two *in vivo* interaction studies are available.

No population pharmacokinetic analysis has been performed as an alternative to specific pharmacokinetic studies. Esmya is only intended for use in females of fertile age, for which PK and clinical studies have been performed. Hence, data on age and gender are considered sufficient. No data with respect to the effects of weight or race on the pharmacokinetics of ulipristal acetate are available. The applicant analysed the influence of weight and Body Mass Index on the trough concentrations in two pivotal clinical studies with two different doses. There was a high variability and, despite the fact that a trend to a higher exposure with higher weight was seen, a clear and relevant relationship was difficult to detect. The clinical relevance of this marginally higher exposure is therefore considered small.

In patients with renal impairment, no dose adjustment in mild or moderate impairment are suggested while Esmya is not recommended in severe renal impairment unless the patient is closely monitored. The recommendation not to use Esmya in severe renal impairment unless the patient is closely monitored is therefore endorsed, in the absence of data. A strict contraindication is not proposed and is not considered warranted.

As no study in subjects with hepatic impairment has been submitted, the applicant will conduct a study of the PK of ulipristal acetate in volunteers with mild, moderate and severe hepatic impairment (PGL-W-001) (included in the RMP). According to the CHMP guideline on the evaluation of pharmacokinetics of medicinal products in patients with impaired hepatic function (CPMP/EWP/2339/02), a study in hepatic impairment should be conducted for a substance like ulipristal acetate since hepatic impairment is likely to significantly alter the pharmacokinetics (especially metabolism and biliary excretion) of the drug and/or its active metabolites, and since a posology adjustment would be likely.

For patients with mild hepatic impairment, no dose adjustment is recommended, while the use in moderate or severe hepatic impairment is not recommended, unless the patient is closely monitored. The recommendation not to use Esmya in moderate and severe hepatic impairment unless the patient is closely monitored is justified, since metabolism appears to be a major elimination route for ulipristal acetate and since the absolute bioavailability is unknown. A strict contraindication in severe hepatic impairment is not considered warranted, since ulipristal acetate is not a substance with a narrow therapeutic window and since 10-fold higher doses (50 mg/day for 10 days) have been administered without serious safety concerns.

The effective dose of ulipristal acetate as emergency contraception product (early pregnancy; within 5 days post-intercourse) is 6 times the dose recommended in uterine fibroids. Use of non-hormonal contraceptive methods is recommended during treatment with Esmya, with a statement of the SmPC that concomitant use of Esmya is likely to reduce progestagen efficacy. No cases of unintended pregnancy during ulipristal acetate treatment were reported in Phase II/III studies of ulipristal acetate for treatment of symptomatic fibroids in patients eligible for surgery.

The study also highlights the need for more understanding of the endometrial effects during long-term treatment with ulipristal, beyond 3 months. Histopathological evaluation of endometrial biopsies in women treated with ulipristal is very difficult as the patterns found apparently do not follow that seen during other hormonal treatment. The 6 months post-treatment follow data from the Phase III study and its extension (PGL09-026 and PGL09-027 respectively) and the follow-up of the proposed non-interventional study (PGL10-014) will supply more long term data on the endometrial safety of Esmya administration up to 12-month post treatment, as detailed in the RMP (see section 2.7. Pharmacovigilance).

Based on the clinical pharmacology data submitted in this dossier, the Product Information has been revised as follows:

Section 5.2 of the SmPC includes information on the following pharmacokinetic properties of ulipristal acetate:

Following oral administration of a single dose of 5 or 10 mg, ulipristal acetate is rapidly absorbed, with a C_{max} of 23.5 ± 14.2 ng/ml and 50.0 ± 34.4 ng/ml occurring approximately 1 h after ingestion, and with an $AUC_{0-\infty}$ of 61.3 ± 31.7 ng/ml 134.0± 83.8 ng.h/ml, respectively. Ulipristal acetate is rapidly transformed into a pharmacologically active metabolite with a C_{max} of 9.0 ± 4.4 ng/ml and 20.6 ± 10.9 ng/ml also occurring approximately 1 h after ingestion, and with an $AUC_{0-\infty}$ of 26.0 ± 12.0 ng/ml and 63.6 ± 30.1 ng.h/ml respectively.

Administration of ulipristal acetate (30 mg tablet) together with a high-fat breakfast resulted in approximately 45% lower mean C_{max}, a delayed t_{max} (from a median of 0.75 hours to 3 hours) and 25% higher mean $AUC_{0-\infty}$ compared with administration in the fasted state. Similar results were obtained for the active mono-N-demethylated metabolite. This kinetic effect of food is not expected to be of clinical relevance for daily administration of ulipristal acetatetablets.

Ulipristal acetate is highly bound (>98%) to plasma proteins, including albumin, alpha-l-acid glycoprotein, high density lipoprotein and low density lipoprotein.

Ulipristal acetate is readily converted to its mono-N-demethylated and subsequently to its di-N-demethylated metabolites. In vitro data indicate that this is predominantly mediated by the cytochrome P450 3A4 isoform (CYP3A4). The main route of elimination is through faeces and less than 10% is excreted in the urine. The terminal half-life of ulipristal acetate in plasma following a single dose of 5 or 10 mg is estimated to be about 38 hours, with a mean oral clearance (CL/F) of about 100 l/h.

In vitro data indicate that ulipristal acetate and its active metabolite do not inhibit CYP1A2, 2A6, 2C9, 2C19, 2D6, 2E1, and 3A4, or induce CYP1A2 at clinically relevant concentrations. Thus administration of ulipristal acetate is unlikely to alter the clearance of medicinal products that are metabolised by these enzymes. In vitro data indicate that ulipristal acetate and its active metabolite are not P-gp (ABCB1) substrates. The applicant will conduct a Phase I drug-drug interaction study with a sensitive P-gp substrate to look further into the pharmacokinetics of ulipristal acetate (included in the RMP).

No pharmacokinetic studies with ulipristal acetate have been performed in women with impaired renal or hepatic function. Due to the CYP-mediated metabolism, hepatic impairment is expected to alter the elimination of ulipristal acetate, resulting in increased exposure. The applicant will perform a phase I study of the pharmacokinetics of ulipristal acetate in volunteers with mild, moderate and severe hepatic impairment, (PGL-W-001) (included in the RMP).

Section 4.4 of the SmPC note that the use of non-hormonal contraceptive methods is recommended during treatment with Esmya.

Section 4.6 of the SmPC notes the effects of ulipristal acetate on fertility, pregnancy and lactation. Ulipristal acetate is likely to adversely interact with progestagen-only pills, progestagen-releasing devices or combined oral contraceptive pills, therefore, concomitant use is not recommended. Although a majority of women taking a therapeutic dose of Esmya have anovulation, a non hormonal contraceptive method is recommended during treatment. Esmya is contraindicated during pregnancy. There are no or limited amount of data from the use of ulipristal acetate in pregnant women. Although no teratogenic potential was observed, animal data are insufficient with regard to reproduction toxicity. Available toxicological data in animals have shown excretion of ulipristal acetate in milk. It is unknown whether ulipristal acetate is excreted in human milk and a risk to the newborns/infants cannot be excluded. Esmya is contraindicated during breast-feeding. A majority of women taking a therapeutic dose of Esmya have anovulation, however, the level of fertility while taking multiple doses of Esmya has not been studied.

Section 4.2 of the SmPC includes recommendations on special populations such as patients with renal impairment, hepatic impairment and children. No dose adjustment is recommended in patients with mild or moderate renal impairment. In the absence of specific studies, Esmya is not recommended in patients with severe renal impairment unless the patient is closely monitored. No dose adjustment is recommended for patients with mild hepatic impairment. In the absence of specific studies, Esmya is not recommended in patients with moderate or severe hepatic impairment unless the patient is closely monitored. There is no relevant use of Esmya in the paediatric population. The safety and efficacy of Esmya was only established in women of 18 years and older.

2.4.5. Conclusions on clinical pharmacology

The clinical pharmacology data package submitted was considered adequate. As no study in subjects with hepatic impairment has been submitted, the applicant will conduct a study of the PK of ulipristal acetate in volunteers with mild, moderate and severe hepatic impairment (PGL-W-001) (included in the RMP). The applicant will also conduct a Phase I drug-drug interaction study with a sensitive P-gp substrate to look further into the pharmacokinetics of ulipristal acetate.

The ongoing Phase III study (PGL09-026), its extension (PGL09-027) and the follow-up of the proposed non-interventional study (PGL10-014) will provide more long term data on the endometrial safety of Esmya administration up to 12-month post treatment.

The aforementioned post-authorisation measures have been adequately covered in the RMP.

2.5. Clinical efficacy

The efficacy of ulipristal acetate as a treatment of uterine fibroids was assessed in four studies: two pivotal Phase III studies (Study PGL07-021 and Study PGL07-022), and two smaller Phase II studies (Study PGL-N-0287 and Study PGL-N-0090). The table below summarizes the key design characteristics of the efficacy studies.

Table 9. Efficacy study design characteristics

Phase	Study	Design	Treatment Duration	Treatment groups	Dose	N
III	PGL07-021	Double-blind, placebo controlled	12 weeks	Ulipristal acetate[a]	5 mg/day	96
					10 mg/day	98
				Placebo[a]	-	48
	PGL07-022	Double-blind, double-dummy, active comparator controlled	12 weeks	Ulipristal acetate	5 mg/day	102
					10 mg/day	103
				Leuprorelin	3.75 mg once a month[b]	102
II	PGL-N-0287	Double-blind, placebo controlled	12 weeks	Ulipristal acetate	10 mg/day	8
					20 mg/day	6
				Placebo	-	8
	PGL-N-0090	Double-blind, placebo controlled	12-24 weeks[c]	Ulipristal acetate	10 mg/day	13
					20 mg/day	14
				Placebo	-	14

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

b Administered as an intramuscular injection

c Week 12 to Week 24 was an optional, unblinded extension period of ulipristal acetate treatment, which was undertaken by 4 subjects from the placebo group (2 each received ulipristal acetate 10 and 20 mg/day), 3 subjects

2.5.1. Dose response studies

PGL-N-0287

PGL-N-0287 was a randomized, double-blind placebo-controlled Phase II study of the effect of daily administration of 10mg or 20mg ulipristal acetate to reduce fibroid size in otherwise healthy women with symptomatic uterine fibroids requesting a hysterectomy. The first cycle was at baseline after

which treatment continued over three menstrual cycles (or 90-102 days). Subjects were admitted for hysterectomy after the LH surge in the third treatment cycle, or in the follicular phase of the fourth cycle or, if anovulatory, between 90 and 102 days of treatment. Subjects were randomized to one of the following treatments: ulipristal acetate at a dose of 10 mg; ulipristal acetate at a dose of 20 mg; placebo. The primary objective of the study was to compare the effect of daily administration of ulipristal acetate over a period of 10-14 weeks to that of placebo. 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 association. However, the data appear to support an effect of ulipristal acetate in reducing fibroid volume.

PGL-N-0090

Study PGL-N-0090 was a randomized, placebo-controlled, double blind, parallel group Phase II study in regularly menstruating, otherwise healthy women with symptomatic uterine leiomyoma. The study consisted of a baseline cycle and 2 treatment phases, both of a duration of 3 menstrual cycles. During phase 1, subjects received randomized, double-blind treatment including placebo. At the end of this phase, subjects could choose to continue treatment (with the same dose or – if previously placebo – randomize to 10 or 20mg dose) in phase 2 for an additional 3 months or to elect surgery (myomectomy or hysterectomy). The primary objective of this study was to compare the effect of daily administration of ulipristal acetate in cycling women with leiomyomata to reduce leiomyoma size.

Endometrial biopsy results

The endometrial biopsies were taken after 3 - 6 months. No endometrial biopsies were performed during screening. Thirty-four subjects underwent at least one endometrial biopsy during the 2 phases of treatment. Of those, 9 biopsies did not allow for a clear diagnosis. In 4 biopsies hyperplasia were diagnosed. As the scoring system for endometrial biopsies in the Phase II trials did not allow for description of Progesterone Receptor Modulator-Associated Endometrial Changes (PAEC) findings, the Applicant was asked to re-evaluate the 4 cases of endometrial hyperplasia according to the rating scale that includes standard descriptors for PAEC, as was used in the Phase III studies.

These four biopsies were re-evaluated by three expert pathologists blinded for each other´s assessment. No diagnosis of endometrial hyperplasia was made by any of the expert pathologists

The ongoing Phase III study and its extension (PGL09-026 and PGL09-027) and the follow-up of the proposed non-interventional study (PGL10-014) will generate more long term data on the endometrial safety of Esmya administration up to 12-month post treatment.

2.5.2. Main studies

PGL07-021

A Phase III, randomized, parallel group, double-blind, placebo controlled, multi-center study to assess the efficacy and safety of PGL4001 (ulipristal) versus placebo for pre-operative treatment of symptomatic uterine myomas.

Methods

Study Participants

Eligible participants in this study were pre-menopausal women with symptomatic uterine myoma(s), excessive uterine bleeding and anemia for whom a surgical procedure was indicated to treat the myomas (i.e. hysterectomy, myomectomy, uterine artery embolization or endometrium ablation).

Inclusion criteria

In order to be included, subjects fulfilled the following criteria:

- provided written informed consent prior to any study related procedures.
- were a pre-menopausal woman between 18 and 50 years inclusive.
- had a PBAC score >100 during Day 1 to Day 8 of menstruation preceding the baseline visit.
- had myoma-related anemia defined as hemoglobin (Hb) ≤10.2 g/dL. Absence of macrocytic anemia was to be proven by a mean corpuscular volume (MCV) ≤104 fL.
- had a myomatous uterus volume ≤16 weeks.
- had at least one uterine myoma of ≥3 cm diameter in size and no myoma larger than 10 cm diameter in size confirmed by ultrasound.
- were eligible for one of these surgical procedures: i.e. hysterectomy, myomectomy, uterine artery
- embolization or endometrial ablation within 13 weeks and up to 14 weeks from baseline study visit.
- had a clinical breast examination without significant findings at the screening visit.
- had no clinically significant findings at Papanicolaou test (PAP) smear, performed within the past 12 months or at the screening visit.
- if of childbearing potential the subject had to be practicing a non-hormonal method of contraception as listed below:
  - sexual abstinence
  - diaphragms
  - condom or partner with a vasectomy performed at least 6 months prior to the study and confirmed azoospermia.
- if of non childbearing potential, the subject had to have had a tubal ligation sterilization at least two months before study start.
- had a Body Mass Index (BMI) ≥18 and ≤40.

Exclusion criteria

Subjects who fulfilled any of the following criteria were excluded from participation:

- had a history of uterus surgery (except caesarean section or cervical conization), endometrial ablation or uterine artery embolization.
- had a history of or current uterine, cervical, ovarian or breast cancer.

- had a history of atypical hyperplasia or a current endometrium hyperplasia (atypical or non-atypical) or adenocarcinoma or similar lesions in the screening biopsy or in a biopsy performed within the past 6 months.
- had a condition requiring immediate blood transfusion or a level of Hb ≤6 g/dL.
- had a known hemoglobinopathy (i.e. Sickle Cell anemia and Thalassemia).
- had a known severe coagulation disorder
- had a large uterine polyp (>2cm).
- had one or more ovarian cysts ≥4cm in diameter diagnosed by ultrasound (US).
- presented with any metallic, ferro-magnetic or electronic implant and/or device which may interfere with the MRI examination or potentially pose a risk (e.g. internal (implanted) defibrillator, implanted spinal cord stimulator, IVC filters, cochlear (ear) implant, clips used on brain aneurysms, artificial heart valves, implanted drug infusion ports, infusion catheter, IUD, implanted electronic device, including a cardiac pacemaker, artificial limbs or metallic joint prostheses, implanted nerve stimulators, metal pins, screws, plates or surgical staples, metallic foreign body fragments (metal splinter) in orbit, congestive heart failure, claustrophobia, pedicle screws / anterior interbody cages in spine).
- had a history of or current treatment for myoma with a Selective Progesterone Receptor Modulator (SPRM) or a Gonadotropin Releasing Hormone agonist (GnRH-agonist).
- had been taking:
    - treatments with progestins (systemic or progestin releasing intra-uterine system) or an oralcontraceptive: within the month before the screening visit,
    - acetylsalicylic acid, mefenamic acid, anticoagulants such as coumarins and/or antifibrinolytic drugs such as tranexamic acid: within one week before the screening visit,
    - systemic glucocorticoid treatments and/or systemic depot glucocorticoid treatments within one week or two months before the screening visit, respectively.
- was likely to require treatment during the study with drugs that were not permitted by the study protocol: progestins (systemic or progestin releasing intra-uterine system), oral contraceptives, systemic glucocorticoids (oral and injectable), acetylsalicylic acid, and/or mefenamic acid, anticoagulants such as coumarins and/or antifibrinolytic drugs such as tranexamic acid.
- had abnormal hepatic function at study entry (defined as aspartate transaminase (AST), alanine transaminase (ALT), gamma glutamyl transferase (γGT), alkaline phosphatase or total bilirubin above 2 Upper Limit of Normal range (ULN)).
- had a positive pregnancy test at baseline or was nursing or planning a pregnancy during the course of the study.
- had a current (within twelve months) problem with alcohol or drug abuse.
- had a mental condition rendering the subject unable to understand the nature, scope and possible consequences of the study, and/or evidence of an uncooperative attitude.
- had abnormal baseline findings, any other medical condition(s) or psychiatric condition(s) or laboratory findings that, in the opinion of the investigator, might jeopardize the subject's

safety or interfere with study evaluations. This included the use of agents known to induce or inhibit the hepatic cytochrome CYP3A4.

- had an allergy to SPRMs or progestins or any of the ingredients of the study drug tablet (referred to in the Investigator's Brochure)
- was currently enrolled in an investigational drug or device study or had participated in such a study within the last 30 days

Treatments

Subjects were randomized to one of three treatment groups in a 2:2:1 ratio to receive either PGL4001 5 mg, PGL4001 10 mg, or PGL4001 matching placebo.

Part A:

Subjects were treated for up to 13 weeks, and after end-of-treatment assessments at Week 13 subjects still qualifying for surgery underwent hysterectomy, myomectomy, uterine artery embolization or endometrial ablation as determined by the investigator. All subjects underwent a closing Week 17 visit, which concluded Part A of the study.

Part B:

Part B of the study was the follow-up study period without treatment; all subjects were to be seen 3 months and 6 months after the end-of-treatment (Week 13), at Week 26 and Week 38.

Objectives

Efficacy Objectives

Primary objectives

To demonstrate superior efficacy of PGL4001 with concomitant iron administration versus placebo with concomitant iron administration:

- To reduce excessive uterine bleeding prior to surgery
- To reduce total myoma volume prior to surgery.
- To demonstrate superior efficacy of PGL4001 with concomitant iron administration versus placebo with concomitant iron administration in correcting anemia caused by uterine myomas.

Secondary objectives

- To demonstrate improvement in myoma-related symptoms, such as pain.
- To assess PGL4001 capacity to decrease uterine volume.

Exploratory objectives

- the proportion of subjects switched to less invasive surgery or for whom surgery is cancelled due to improved condition at treatment completion,

- the proportion of subjects undergoing blood transfusion, the number of transfusions and volume transfused per subject.

Safety Objectives

- Assess overall safety of ulipristal acetate (PGL4001) in subjects with uterine myomas.

Outcomes/endpoints

Co-Primary efficacy endpoints:

- Percentage of subjects with reduction in uterine bleeding defined as a PBAC score <75 at end-of treatment visit (Week 13 visit)
- Change in total myoma volume assessed by Magnetic resonance Imaging (MRI) from screening to end of treatment visit (Week 13 visit).

Secondary efficacy endpoints:

- change from baseline to Week 5, Week 9, and Week 13 visits in bleeding pattern recorded by subjects using the PBAC.
- change from baseline to Week 5, Week 9 and Week 13 visits in Hb, hematocrit (Hct) and ferritine.
- percentage of subjects with Hb >12 g/dL and Hct >36% at Week 5, Week 9 and Week 13 visits.
- percentage of subjects in amenorrhea at Week 5, Week 9, and Week 13 visits.
- percentage of subjects with a volume reduction of ≥25% of the total myoma volume assessed by MRI at Week 13 visit.
- percentage of subjects with a reduction of ≥25% of uterine volume assessed by MRI at Week 13 visit.
- change from screening to Week 13 visit in uterine volume assessed by MRI.
- change from baseline to Week 5, Week 9, and Week 13 visits in global pain score (Short-form McGill Pain questionnaire).
- change from baseline to Week 13 visit in symptoms related to uterine myomas (Measurement of discomfort due to uterine fibroids questionnaire).
- measurement of pain (McGill Pain Questionniare).
- quality of life (Uterine Fibroids Questionnaire)

Sample size

The sample size calculation was based on both primary efficacy endpoints, and to ensure that there was adequate patient exposure to PGL4001 in order to assess patient safety. The calculation was based on demonstrating superiority of PGL4001 versus placebo with at least 90% power for each of the primary endpoints, using two sided tests with type I error rates of 5%, and a Bonferroni correction for the two dose comparisons.

In order to achieve a power of 90%, the analysis of the total myoma volume required more subjects than the analysis of percentage of subjects with PBAC <75 at end-of-treatment visit, so the sample size calculation was based on this endpoint.

With an estimated 10% on-treatment drop-out rate, 240 patients were required to be randomized to ensure adequate power (96 subjects for each treatment group and 48 subjects in placebo). 242 subjects were actually recruited in 35 sites, in six countries.

Randomisation

Subjects were randomly assigned to one of three treatment groups in a 2:2: 1 ratio: placebo, PGL4001 5 mg and PGL4001 10 mg.

Prior to the start of the study, a randomization list was generated to be transmitted to the assigned clinical packaging organization for labeling and to a fully web-integrated interactive voice/web response system.

The randomization list and/or the electronic file were secured in a locked cabinet and/or an electronic file with restricted access to only the designated personnel directly responsible for labeling and handling the study medication, until the study database was locked and ready to be un-blinded.

Kit numbers indicated on the list started from 3001, 3002, 3003 etc. (4-digit) and corresponded to the kit number indicated on the label of the study drug. Complete blocks of treatment materials were sent to the investigational centers. Subjects were randomized following a stratification by hematocrit (Hct) value (measured at Screening) and ethnicity in order to avoid any unbalance between treatment groups as follows

- Hct ≤28%, and Hct >28%
- Black African women or other ethnicities

Blinding (masking)

The designed study was considered to be double blind. The randomization list was secured in a locked cabinet and/or a computer file with restricted access to only the designated personnel directly responsible for labelling and handling the study medication.

All evaluations conducted as part of the study were performed by individuals who were blinded to the treatment allocation. The study blind could be broken for an individual subject only in the case of an emergency when knowledge of the IMP was essential for the clinical management of the subject.

After the last subject had completed Part A of the protocol, the treatment groups were un-blinded, and the results up to Week 17 were analyzed. Once the last subject has completed Part B of the protocol, results of study Weeks 26 and 38 will be analyzed.

Statistical methods

All statistical hypothesis tests and confidence intervals performed were two sided, using a 5% level of statistical significance. As comparisons involve two dose levels, a Bonferroni correction for the hypothesis tests and confidence intervals was used. The Intent-to-Treat (ITT) population was the population of primary interest for the efficacy analyses. When the assumptions of any of the

parametric analysis such as normality or variance heterogeneity were deemed invalid, then appropriate non-parametric methods were used instead.

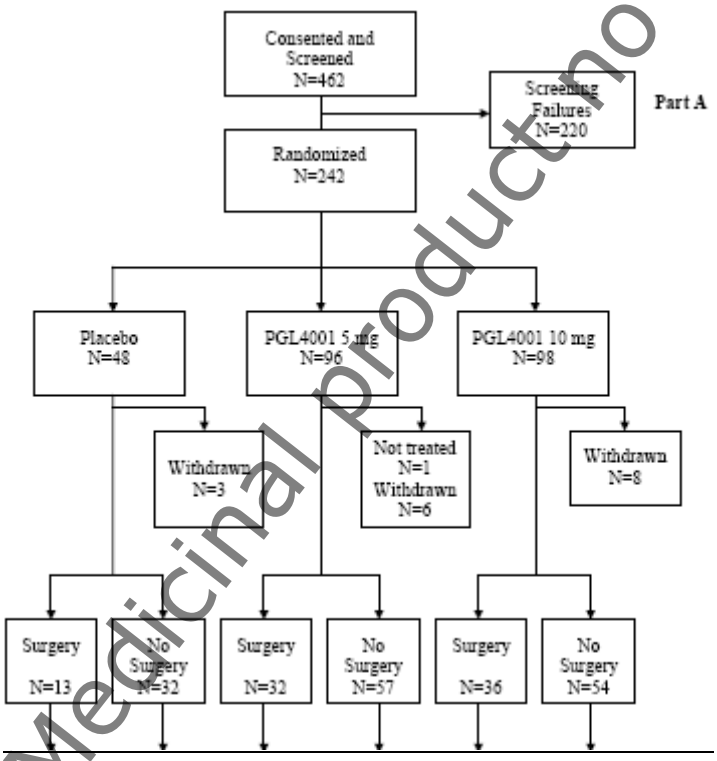
The primary objective of demonstrating superior efficacy of PGL4001 versus placebo to reduce excessive uterine bleeding was assessed by testing the null hypothesis that there is no difference in the percentage of subjects with PBAC <75 at end-of-treatment visit (Week 13 visit) for PGL4001 compared with placebo. The hypothesis was tested via a Cochran-Mantel-Haenszel test.

The primary objective of demonstrating superior efficacy of PGL4001 versus placebo to reduce total myoma volume prior to surgery was assessed by testing the null hypothesis that there is no difference in the average change in total myoma volume assessed by MRI from screening to end of treatment visit (Week 13 visit) for PGL4001 compared with placebo. The hypothesis was tested via analysis of covariance, after log transforming the data.

A successful outcome was deemed to occur if at least one of the 5 mg or 10 mg PGL4001 treatments results in a statistically significant improvement over placebo with regards to both endpoints

Results

Participant flow



Recruitment

The study period was from 31 October 2008 to 17 Aug 2010. This was a multinational study planned to be conducted in 30 sites. Thirty nine sites were initiated in 6 countries but only 38 sites actively recruited.

Conduct of the study

Individual major protocol deviations were reviewed in order to identify subjects who would need to be excluded from the PP population. If the reason a subject did not meet protocol compliance >80% was due to early withdrawal from the study then the subjects would be excluded from the PP population, but that this was not to be considered as a major protocol violation.

Due to the unexplained repeated receipt of clotted blood samples, two subjects (141/1050 and 144/1087) were included based on local laboratory analyses for hematology parameters at screening.

A summary of the major protocol deviations is listed in the table below. A total of 2 (0.8%) subjects had a major protocol deviation, both of whom were in the PGL4001 5 mg group.

Table 10. Summary of Major Protocol Deviations (Treated Subjects)

	Treatment Group			
	Placebo (N=48)	PGL4001 5mg (N=95)	PGL4001 10mg (N=98)	Total (N=241)
Deviation Type				
At Least One Major Deviation	0	2 (2.1%)	0	2 (0.8%)
Inclusion / Exclusion Criteria	0	1 (1.1%)	0	1 (0.4%)
Received Incorrect Treatment Kit	0	0	0	0
Treatment Compliance	0	0	0	0
Last non-missing on-treatment PBAC data is recorded on less than or equal to day 56	0	0	0	0
Screening PBAC data was completed retrospectively using different towels/tampons than those provided specifically for the study	0	0	0	0
Prohibited Concomitant Medication	0	0	0	0
Other	0	1 (1.1%)	0	1 (0.4%)

Baseline data

The demographic characteristics of all randomized subjects for the safety population are presented by treatment group in the table below. The characteristics were similar between treatment groups, and also between analysis populations. The majority of subjects in the study were of white origin (88%), and of childbearing potential (92.1%), where non-childbearing potential was defined as having undergone a tubal ligation prior to study start.

Table 11. Summary of demographic characteristics at Baseline Safety Population

Variable Parameter	Study PGL07-021			
	Placebo (N=48)	Ulipristal acetate 5 mg/day (N=95)	Ulipristal acetate 10 mg/day (N=98)	Total (N=241)
Race N (%)				
Black	0	0	0	0
White	41 (85.4%)	84 (88.4%)	87 (88.8%)	212 (88.0%)
Asian	7 (14.6%)	11 (11.6%)	11 (11.2%)	29 (12.0%)
Hispanic	0	0	0	0
Other	0	0	0	0
Age [years] (n)	48	95	98	241
Mean (SD)	41.6 (5.6)	41.2 (5.9)	42.0 (5.5)	41.6 (5.7)
Min/Max	26 / 50	24 / 50	23 / 50	23 / 50
Height [cm]	48	95	98	241
Mean (SD)	162.3 (6.6)	164.3 (6.5)	163.9 (6.1)	163.7 (6.4)
Min/Max	143 / 176	150 / 178	145 / 178	143 / 178
Weight [kg] (n)	48	95	98	241
Mean (SD)	64.7 (12.5)	70.1 (13.6)	67.1 (10.3)	67.8 (12.2)
Min/Max	45.0 / 106.5	42.0 / 120.0	48.9 / 95.0	42.0 / 120.0
BMI [kg/m2] (n)	48	95	98	241
Mean (SD)	24.6 (4.4)	25.9 (4.6)	25.0 (3.9)	25.3 (4.3)
Min/Max	18.0 / 40.1	18.1 / 39.2	18.1 / 37.6	18.0 / 40.1
Of Childbearing Potential N (%)	43 (89.6%)	87 (91.6%)	92 (93.9%)	222 (92.1%)

Numbers analysed

A total of 242 patients were randomized. One subject from the PGL4001 5 mg group did not receive any treatment as she had entered menopause.

All subjects who were randomized into the study and who used the trial medication at least once were considered evaluable for the safety population. In the event that a subject received study medication other than that to which she was randomized, the analysis was performed using the treatment actually received. Any subject who received trial medication from more than one treatment group was excluded from the safety population. A total of 241 subjects were included in the safety population: placebo (N=48), PGL4001 5 mg (N=95) and PGL4001 10 mg (N=98).

The ITT population was defined as all randomized subjects who used the trial medication at least once, and who had post-baseline, that is, on-treatment, efficacy data for at least one efficacy endpoint. In the event that a subject received study medication other than that to which she was randomized, the analysis was to be performed using the treatment group to which she was randomized, rather than by

the actual treatment she was administered. The ITT population was a subset of the Safety population and consisted of 237 subjects: placebo (N=48), PGL4001 5 mg (N=95) and PGL4001 10 mg (N=94).

The PP population was a subset of the ITT population. Subjects who withdrew early from the study and as a consequence had a protocol compliance <80% were excluded from the PP population. In addition, subjects with one or more major protocol deviations were excluded from the PP population. Protocol deviations including poor compliance occurring during Part A were determined before database lock at the end of Part A and un-blinding of the study. The PP population used for the additional analyses at the end of Part B will be the same as that used for Part A, in order to keep the analyses consistent, and to prevent any bias in selecting the population after un-blinding. The PP population consisted of 216 subjects: placebo (N=45), PGL4001 5 mg (N=85) and PGL4001 10 mg (N=86).

Eighteen subjects discontinued the study prior to Week 17 due to, lack of efficacy (N=2), subject request (N=9), protocol deviation (N=2), lost to follow-up (N=4) and other reason (N=1).

Outcomes and estimation

Primary endpoints

Analysis of Uterine Bleeding: ITT population

The primary goal of treatment in this study was to reduce the PBAC score to <75 over the period of an entire month, which is considered to be within the normal range of menstrual blood loss, i.e. to reduce excessive uterine bleeding caused by uterine myomas, and thereby also reduce myoma-related symptoms and consequent need for surgery.

The PBAC was completed from Day 1 of menstruation to Day 28 (inclusive) during the screening period, and continuously from Day 1 of menstruation on, or just before treatment, to the last day of treatment (inclusive). It was reported at baseline, Week 5, Week 9 and Week 13 visits. The PBAC score for a specific four week period was calculated by multiplying the number of occurrences of each item in the chart by the items' score, and summing up the results for 28 days. Days where 'no bleeding' had been recorded have a score of zero for that day.

The percentage of subjects with reduction of uterine bleeding defined as PBAC score <75 at end-of-treatment visit (Week 13 visit) are given in table below.

Table 12. Mean baseline PBAC scores and numbers and percentage of subjects with PBAC score <75 at week 13 (Study PGL07-021, ITT population, LOCF)

PBAC	Placebo	Ulipristal acetate 5mg/day	Ulipristal acetate 10 mg/day
Baseline (n)	48	95	94
Mean PBAC score (SD)	460 (293)	487 (320)	411 (250)
Median PBAC score (min, max)	376 (119, 1284)	386 (118, 1645)	330 (102, 1570)
Week 13 (n)	48	94	93
Number (%) of Subjects with PBAC Score < 75	9 (18.8%)	86 (91.5%)	86 (92.5%)
Difference vs. control	-	72.7%	73.7%
95% CI	-	55.1, 83.2	56.2, 84.0
p-value		p <0.001	p <0.001

Analysis of Uterine Bleeding: Pre-operative population

In a sub-analysis of the pre-operative population (subjects who underwent surgery after treatment with ulipristal acetate), the evidence of superiority towards placebo and non-inferiority towards leuprorelin is maintained. In the placebo controlled study PGL07-021 at Week 13, the percentage of pre-surgical subjects with PBAC score < 75 was far greater with ulipristal acetate 5 and 10 mg (85.4% and 89.8% respectively) than with placebo (21.1%) ($p < 0.001$). This represented a difference (95% CI) compared with placebo of 64.3% (34.0, 80.3) for ulipristal acetate 5 mg and 68.7% (39.7, 83.7) for ulipristal acetate 10 mg.

Analysis of Total Myoma Volume: ITT population

In this study the co-primary efficacy endpoint was the evaluation of decrease in uterine myoma volume as measured by centralized MRI. The technique of MRI to measure uterine volume was chosen rather than ultrasound, as ultrasound can be associated with high variability between evaluators.

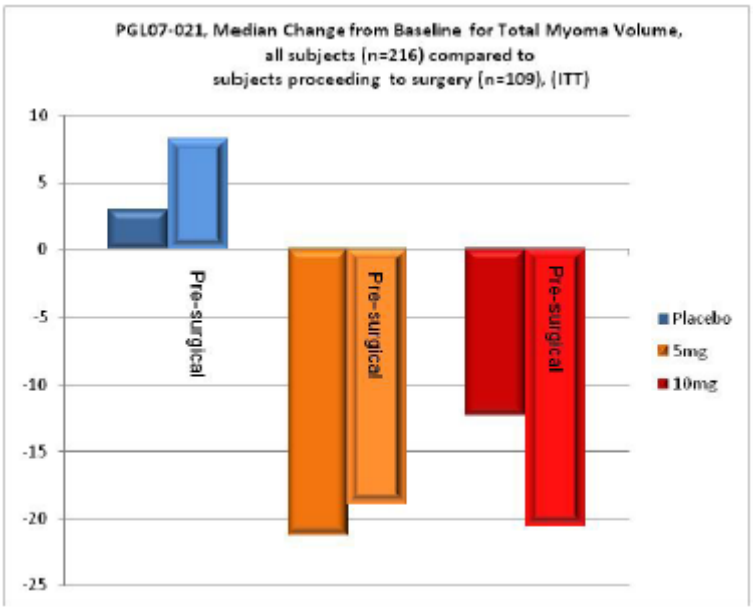
Table 13. Mean volumes and percentage change in total fibroid volume from screening to Week 13 (Study PGL07-021, ITT population) assessed by MRI

Total Fibroid Volume		Placebo N = 48	Ulipristal acetate 5 mg/day N = 95	Ulipristal acetate 10 mg/day N = 94
Raw data cm^3				
Screening	n	45	89	82
	Mean (SD)	**136.0 (191.4)**	**142.5 (133.3)**	**134.3 (151.0)**
	Median (min, max)	61.9 (0.4, 1053.1)	100.7 (0.5, 616.6)	96.7 (0.6, 966.1)
Week 13	n	45	86	82
	Mean (SD)	**133.8 (174.0)**	**136.7 (207.2)**	**128.5 (193.9)**
	Median (min, max)	59.5 (0.0, 731.0)	65.8 (0.0, 1520.6)	71.9 (0.0, 1325.6)
% change, Screening to Week 13				
Mean		0.9	-14.7	-16.0
Median (min, max)		3.0 (-100.0, 134.8)	-21.2 (-100.0, 223.4)	-12.3 (-100.0, 146.6)
Difference[a]			**-22.6**	**-18.2**
95% CI			-36.1, -8.2	-33.0, -5.2
p-value[b]			**0.002**	**0.006**

Analysis of Total Myoma Volume: Pre-operative population

When restricting to the pre-operative population (109 subjects), the total fibroid volume increased in a comparable order of magnitude from Screening to Week 13 with placebo (mean [median] percentage increase of -1.9% [8.3%]), and decreased with ulipristal acetate 5 mg (-13.0% [-19.0%]) and 10 mg (-17.8% [-20.6%]). Although ulipristal acetate was equally effective in reducing myoma volume in the pre-operative patient population, there were only 18 subjects in the placebo group contributing data at week 13, and the reduction of sample size resulted in a loss of statistical significance for 5 mg ulipristal acetate (Median difference of - 21.9%, 95% CI: -39.3%, 7.5%, $p = 0.157$) and 10 mg (Median difference of -18.9%, 95% CI: -43.6%, 3.5%, $p = 0.079$). These results are illustrated in the Figure 1 below.

Figure 1. Median Change from Baseline for Total Myoma Volume, PGL07-021



Secondary endpoints

Key results of secondary efficacy endpoints in Study PGL07-021 in table below.

The mean and median Hb, Hct and ferritine values were similar for all three treatment groups at screening as well as at baseline. The eligibility criterion of Hb ≤10.2 g/dL was evaluated at the screening visit. A quarter of the subjects exceeded this criterion at the baseline visit. The prescription of iron supplements during the screening period was allowed, being standard clinical practice.

Table 14. Key results of secondary efficacy endpoints in Study PGL07-021, ITT population

Parameter		PGL07-021 (ITT Population		
		Placebo	Ulipristal acetate	
		N = 48	5 mg/day N = 95	10 mg/day N = 94
Median Change from Baseline in **PBAC** at Week 13[a]		-59	**-329**	**-326**
n (%) subjects in **Amenorrhea** at Week 13[a]		3 (6.3)	**69 (73.4)**	**76 (81.7)**
LS Mean Change from Baseline at Week 13 in:	**Hb** (g/dL)	3.1	**4.1**	**4.1**
	Hct (%)	7.4	**10.0**	**10.0**
	Ferritine (u/L)	21.4	26.1	26.4
n (%) subjects with **Hb >12 g/dL and Hct >36%**	Baseline	1 (2.2)	4 (4.5)	5 (5.6)
	Week 13[a]	37 (77.1)	81 (85.3)	84 (89.4)
LS Mean $\log_{10}$ change in **uterine volume,** Screening to Week 13		0.01	**-0.07**	**-0.07**
n (%) with **Uterine volume** reduction ≥25%		3 (6.4)	**30 (34.1)**	**24 (28.2)**
N (%) with **total fibroid volume** reduction ≥25%		8 (17.8)	**35 (41.2)**	**33 (41.3)**
LS mean $\log_{10}$ change in **volume of 3 largest fibroids** from Screening to Week 13		-		
SF-MPQ median change from Baseline at Week 13[a]	Part A	-2.5	-5.0	**-5.6**
	Part B (VAS)	-16.5	-30.0	-27.0
	Part C (PPI)	-1.0	-1.0	-1.0
UFS-QoL LS mean change from baseline at Week 13[a]	Symptom Severity	-		
	HRQL Total Score			
Measurement of Discomfort due to Uterine Fibroids Questionnaire, median change from Baseline, Week 13		-6.0	**-9.0**	**-11.0**

Bold values indicate that there was a significant difference between ulipristal acetate vs. Placebo. In study PGL07-021 it was always in favour of ulipristal acetate.

Pain

At baseline, the different pain scores in all three groups, showed values in the lower half of the rating scales. There was a slightly higher pain score at baseline in the placebo group compared to the ulipristal acetate groups. All treatment groups experienced a decrease in levels of pain as assessed by the SF-MPQ at week 13. In the SF-MPQ analyses a statistically significant effect on pain score was only seen for ulipristal acetate 10 mg vs placebo (p=0.037) at week 13.

Table 15: Summary of SF-MPQ (ITT population) Study PGL07-021

Pain score	**Placebo Mean (Median)**	**Ulipristal acetate 5mg Mean (Median)**	**Ulipristal acetate 10 mg Mean (Median)**
SF-MPQ (Part A) Baseline	10.83 (8.50)	9.64 (6.50)	10.17 (8.00)

Pain score	Placebo Mean (Median)	Ulipristal acetate 5mg Mean (Median)	Ulipristal acetate 10 mg Mean (Median)
SF-MPQ (Part A) Week 13	6.74 (4.17)	3.01 (1.0)	3.26(1.0)
VAS (Part B) Baseline	46.69 (49.50)	42.33 (39.00)	41.34 (39.00)
VAS (Part B) Week 13	27.48(20.50)	11.35(2.50)	11.95(5.50)
PPI (Part C) Baseline	1.48 (1.0)	1.16(1.0)	1.10(1.0)
PPI (PartC) Week13	0.52(0.00)	0.31(0.00)	0.41(0.00)

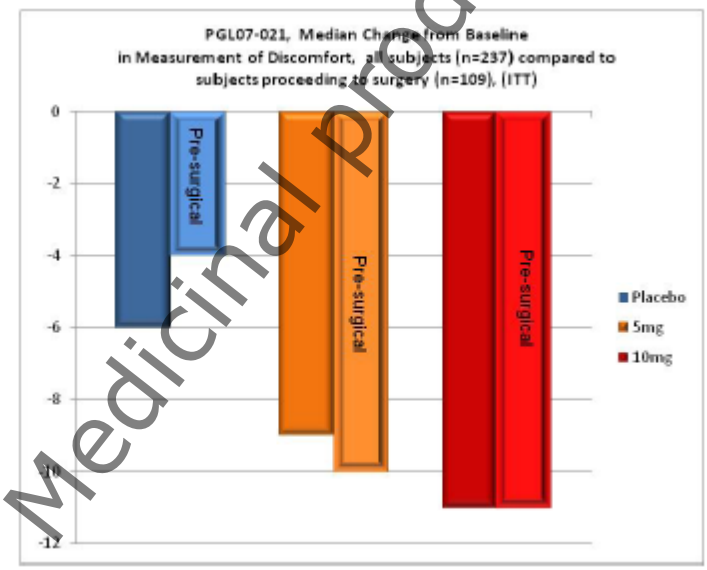
Improvement of Quality of Life

A discomfort questionnaire derived from the validated UFS-QoL was used as there are no versions of the validated fibroid specific UFS-QoL in countries participating to the study. Women were asked to rate the discomfort experienced due to seven different symptoms of uterine fibroids during the previous 3 months.

For the pre-operative population, mean (median) Baseline scores were comparable to the total study population with a score of 16.5 (17) for the placebo group, 15.8 (16) for the ulipristal acetate 5 mg group and a score of 15.2 (16) for the ulipristal acetate 10 mg group.

Comparably to the total study population, there was a statistically significantly greater improvement (decrease) in median total score on the Measurement of Discomfort due to Uterine Fibroid questionnaire from Baseline to Week 13 with ulipristal acetate 5 mg (-10.0, p = 0.021) and 10 mg (-11.0, p < 0.042) compared with placebo (-4). These results are illustrated in the Figure 2 below.

Figure 2. Median Change from Baseline in Measurement of Discomfort, PGL07-021

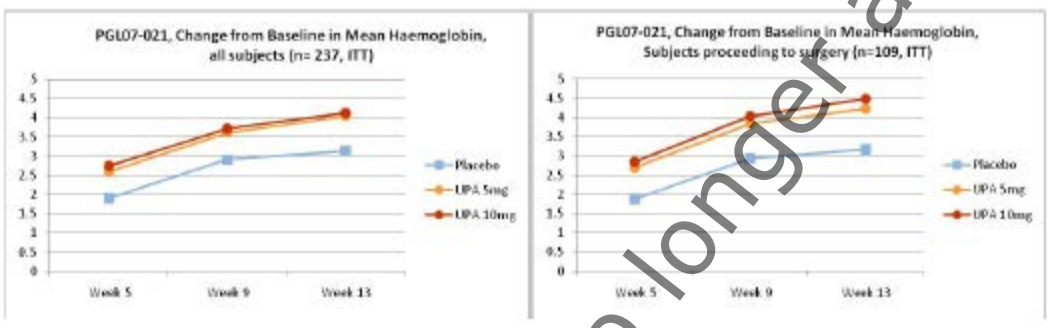


Improvement of Anaemia

Patients were to be anaemic for being eligible (Hb < 10.2 g/dl at screening). Haemoglobin (Hb) levels were compared in the overall and the pre-operative population. The mean (median) Hb values were similar for all three treatment groups of the overall population at baseline (Range from 9.3 to 9.6 (8.9 to 9.2 g/dl). As all subjects received concomitantly iron due to the study inclusion criterion of anaemia, there was an LS mean increase from Baseline for the Hb in all three treatment groups. The increase in Hb from Baseline was statistically significantly larger with both doses of ulipristal acetate compared with placebo at all timepoints from Week 5 onwards (range of p values 0.002 to < 0.001).

The pre-operative population was comparable to the overall population with regards to Baseline Hb mean (median) values (Range from 9.0 to 9.6 g/dl (9.1 to 9.7 g/dl)). Similarly, the LS mean increase in Hb from Baseline was consistently statistically significant for both ulipristal acetate groups from Week 5 onwards (range of p-values 0.010 to < 0.001). No difference between the overall study population and the pre-operative population was observed. These results are illustrated in the Figure X

Figure 3. Change from Baseline in Mean Haemoglobin, PGL07-021



Ancillary analyses

Exploratory efficacy endpoints

Blood transfusions

No blood transfusions occurred during the treatment period up to week 13.

One subject received a blood transfusion during Part A of the study. The subject, in the PGL4001 5 mg group, received 1050 mL of red blood cells on the day after her last intake of study medication. The transfusion occurred on the same day that the woman had a laparoscopic hysterectomy.

Proportion of subjects for whom surgery is cancelled because of improvement of symptoms, and proportion of subjects switched to less invasive surgery

There was no significant difference between the treatment groups concerning cancelled surgery or less invasive surgery. However, the greatest proportion of cancelled surgery (73% vs 66-62%) as well as less invasive surgery (77% vs 69-70%) was found in the placebo group after completion of Part A of the study, i.e. up to 4 week following the end of study treatment (week 17). This difference between placebo and the treatment groups in cancellation of surgery was smaller by the end of Part B (i.e. up to 6 months following the end of treatment): 58% vs 46-56%.

Table 16. Analysis of Surgery part A (ITT Population)

	Treatment Group			
	Placebo (N=48)	PGL4001 5 mg (N=95)	PGL4001 10 mg (N=94)	Total (N=237)
Missing	0 (0.0%)	2 (2.1%)	0 (0.0%)	2 (0.8%)
Non-Missing	48 (100.0%)	93 (97.9%)	94 (100.0%)	235 (99.2%)
Surgery Cancelled (1)	35 (72.9%)	61 (65.6%)	58 (61.7%)	154 (65.5%)
Difference		-7.3%	-11.2%	
(PGL4001 - Placebo) 95% CI (3)		-23.8%, 11.6%	-27.6%, 7.9%	
p-value (4)		0.750	0.373	
Planned and Completed not 'Other' (1)	48 (100.0%)	93 (100.0%)	94 (100.0%)	235 (100.0%)
Less Invasive Surgery (2)	37 (77.1%)	65 (69.9%)	65 (69.1%)	167 (71.1%)
Difference		-7.2%	-7.9%	
(PGL4001 - Placebo) 95% CI (3)		-22.8%, 11.2%	-23.5%, 10.5%	
p-value (4)		0.727	0.648	

Study PGL07-022

A Phase III, randomized, parallel group, double-blind, double-dummy, active comparator-controlled, multi-center study to assess the efficacy and safety of PGL4001 (ulipristal) versus GnRH-agonist (leuprorelin 3.75mg) for pre-operative treatment of symptomatic uterine myomas.

Methods

Study Participants

Eligible patients in this study were pre-menopausal women with symptomatic uterine myoma(s) and excessive uterine bleeding (PBAC score >100) for whom a surgical procedure was indicated to treat the myomas (i.e. hysterectomy, myomectomy, uterine artery embolization or endometrium ablation).

Inclusion criteria

In order to be included, subjects fulfilled the following criteria:

- provided written informed consent prior to any study related procedures.
- were a pre-menopausal woman between 18 and 50 years inclusive.
- had a PBAC score >100 during day 1 to day 8 of menstruation preceding the baseline visit.
- had a myomatous uterus volume ≤ 16 weeks.
- had at least one uterine myoma of ≥ 3 cm diameter in size and no myoma larger than 10 cm diameter in size diagnosed by ultrasound.
- were eligible for one of these surgical procedures: i.e. hysterectomy, myomectomy, uterine artery embolization or endometrium ablation within 13 weeks and up to 14 weeks from baseline study visit.
- had a clinical breast examination without significant findings at the screening visit.

- had no clinically significant findings at Papanicolaou test (PAP) smear, performed within the past 12 months or at the screening visit.
- if of childbearing potential the subject had to be practising a non-hormonal method of contraception as listed below:
    - sexual abstinence
    - diaphragms
    - condom or partner with a vasectomy performed at least 6 months prior to the study and confirmed azoospermia.
- if of non childbearing potential, the subject had to have had a tubal ligation sterilization at least two months before study start.
- had a Body Mass Index (BMI) ≥ 18 and ≤ 40.

Exclusion criteria

Subjects who fulfilled any of the following criteria were excluded from participation:

- had a history of uterus surgery (except caesarean section or cervical conisation), endometrial ablation or uterine artery embolization.
- had a history of or current uterine, cervical, ovarian or breast cancer.
- had a history of atypical hyperplasia or a current endometrium hyperplasia (atypical or no atypical) or similar lesions in the screening biopsy or in a biopsy performed within the past 6 months.
- had a condition requiring immediate blood transfusion or a level of hemoglobin (Hb) ≤ 6 g/dL.
- had a known hemoglobinopathy (i.e. Sickle Cell anemia and Thalassemia).
- had a known severe coagulation disorder.
- had a large uterine polyp (> 2cm).
- had one or more ovarian cysts ≥ 4cm in diameter diagnosed by ultrasound (US).
- had a history of or current treatment for myoma with a Selective Progesterone Receptor Modulator (SPRM) or a GnRH-agonist.
- had been taking:
    - treatments with progestins (systemic or progestin releasing intra-uterine system) or an oral contraceptive: within the month before the screening visit,
    - acetylsalicylic acid, mefenamic acid, anticoagulants such as coumarins and/or antifibrinolytic drugs such as tranexamic acid: within one week before the screening visit,
    - systemic glucocorticoid treatments and/or systemic depot glucocorticoid treatments within one week or two months before the screening visit, respectively.
- was likely to require treatment during the study with drugs that were not permitted by the study protocol: progestins (systemic or progestin releasing intra-uterine system), oral

contraceptives, systemic glucocorticoids (oral and injectable), acetylsalicylic acid, mefenamic acid, anticoagulants such as coumarins and/or antifibrinolytic drugs such as tranexamic acid.

- had a history of or known current osteoporosis.
- had abnormal hepatic function at study entry (defined as aspartate transaminase (AST), alanine transaminase (ALT), gamma glutamine transferase (γGT), alkaline phosphatase or total bilirubin above 2 Upper Limit of Normal range (ULN)).
- had a positive pregnancy test at baseline or was nursing or planning a pregnancy during the course of the study.
- had a current (within twelve months) problem with alcohol or drug abuse.
- had a mental condition rendering the subject unable to understand the nature, scope and possible consequences of the study, and/or evidence of an uncooperative attitude.
- had abnormal baseline findings, any other medical condition(s) or psychiatric condition(s) or laboratory findings that, in the opinion of the investigator, might jeopardize the subject's safety or interfere with study evaluations.
- had an allergy to GnRH-agonist, SPRMs or progestins or any of the ingredients of the study drug tablet (referred to in the Investigator's Brochure)
- was currently enrolled in an investigational drug or device study or had participated in such a study within the last 30 days

Treatments

Subjects were randomized to one of three treatment groups in a 1:1:1 ratio to receive:

• either oral PGL4001 5mg + intramuscular injection of saline solution

• either oral PGL4001 10mg + intramuscular injection of saline solution

• either oral PGL4001 matching placebo + intramuscular injection of leuprorelin 3.75mg

Part A:

Subjects were treated for up to 13 weeks, and after end-of-treatment assessments at Week 13 subjects still qualifying for surgery underwent hysterectomy, myomectomy, uterine artery embolization or endometrium ablation as determined by the investigator. All subjects underwent a closing Week 17 visit, which concluded Part A of the study.

Part B:

Part B of the study was the follow-up study period without treatment; all subjects were to be seen 3 months and 6 months after the end-of-treatment (Week 13), at Week 26 and Week 38.

Objectives

Efficacy Objectives

Primary objective:

- To demonstrate non inferior efficacy of PGL4001 versus Gonadotropin Releasing Hormone (GnRH)-agonist to reduce, prior to surgery, excessive uterine bleeding caused by uterine myomas.

Secondary objectives:

- To demonstrate improvement over baseline in myoma-related symptoms such as impaired Quality of Life (QOL) and pain, and to assess PGL4001 capacity to decrease uterine volume as well as volume of the three largest myomas.

Exploratory objectives:

- To assess the proportion of subjects switched to less invasive surgery or for whom surgery was cancelled due to improved condition at treatment completion,
- To assess the proportion of subjects undergoing blood transfusion, the number of transfusions and volume transfused per subject.

Safety Objectives

Primary objective:

- To demonstrate superior safety and tolerance of PGL4001 versus GnRH-agonist regarding castration-related symptoms and their consequences of which the principal parameters are serum estradiol levels and hot flushes.

Secondary objective:

- To assess overall safety of PGL4001 in subjects with uterine myomas.

Outcomes / endpoints

Primary efficacy endpoint

- the percentage of subjects with reduction of uterine bleeding defined as a PBAC score < 75 at end-of-treatment visit (Week 13 visit).

Secondary efficacy endpoints

- change from baseline to Week 5, Week 9, and Week 13 visits in bleeding pattern recorded by subjects using the PBAC.
- change from baseline to Week 5, Week 9 and Week 13 visits in hemoglobin (Hb), hematocrit (Hct) and ferritine.
- percentage of subjects in amenorrhea at Week 5, Week 9, and Week 13 visits.
- change from screening to Week 13 visit in the total volume of the three largest myomas assessed by ultrasound (US).

- change from screening to Week 13 visit in uterine volume assessed by US.
- change from baseline to Week 5, Week 9, and Week 13 visits in global pain score (Short-form Mc Gill Pain questionnaire [SF-MPQ]).
- change from baseline to Week 13 visit in Uterine Fibroid Symptom and health-related Quality of Life (UFS-QOL) score.

Sample size

The sample size calculation was based on the primary efficacy endpoint, the primary safety endpoints, and to ensure that there was adequate subject exposure to PGL4001 in order to assess overall subject safety. The efficacy calculation was based on demonstrating non-inferior efficacy of PGL4001 versus GnRH-agonist with at least 90% power, using a one-sided confidence interval with type I error rate of 2.5%, and a Bonferroni correction for the two dose comparisons, with a pre-specified non-inferiority margin of 20%.

The safety calculation was based on demonstrating superior safety of PGL4001 versus GnRH-agonist with at least 90% power, using two-sided tests with type I error rate of 5%, and a Bonferroni correction for the two dose comparisons.

For the primary efficacy endpoint, assuming that the PGL4001 and GnRH-agonist response rates are both 85% produces a required sample size of 82 subjects in each treatment group (246 subjects in total).

For the primary safety endpoint serum E2 levels, the analysis was conducted after taking logarithms of the data, which produced a required sample size of 27 subjects in each treatment group.

For the primary safety endpoint percentage of subjects reporting moderate or severe hot flushes as adverse events, assuming a percentage of subjects of 20% for PGL4001, and 65% for GnRH-agonist produced a required sample size of 32 subjects in each treatment group. A larger sample size was needed to satisfy the efficacy objective compared with the safety objective. In order to be conservative and ensure sufficient subject exposure for an overall safety assessment as well, 300 subjects were randomized (100 per treatment group).

Randomisation

Prior to the start of the study, a randomization list was generated to be transmitted to the assigned clinical packaging organization for labelling and to a fully web-integrated interactive voice web response system. The randomization list and/or the electronic file were secured in a locked cabinet and/or an electronic file with restricted access to only the designated personnel directly responsible for labelling and handling the study medication, until the study database was locked and ready to be unblinded.

Kit numbers indicated on the list started from 7001, 7002, 7003 etc. (4-digit) and corresponded to the kit number indicated on the label of the study drug. Complete blocks of treatment materials were sent to the investigational centers.

Subjects were randomized to one of three treatment groups in a 1:1:1 ratio, following a stratification process for avoiding any ethnic imbalance between treatment groups for Black African women or other ethnicities.

Blinding (masking)

The designed study was considered to be double blind, double-dummy. Prior to initiation of the study, study materials were determined to be different in appearance and route of administration. In order to preserve the blind, subjects participating in the study were randomized to receive either PGL4001 5 mg, PGL4001 10 mg, or matching placebo to be administered orally, once daily for up to 13 weeks and received a concomitant intramuscular injection of 3.75 mg leuprorelin or saline solution at each scheduled visit up to Week 13 visit. Leuprorelin or saline solution injections were administered by an independent study nurse. An independent study monitor at each clinical site checked all investigational medicinal products dispensed and returns (both unused and used tablets) during the entire study period.

The randomization list was secured in a locked cabinet and/or a computer file with restricted access to only the designated personnel directly responsible for labelling and handling the study medication.

All evaluations conducted as part of the study were performed by individuals who were blinded to the treatment allocation. The study blind could be broken for an individual subject only in the case of an emergency when knowledge of the IMP was essential for the clinical management of the subject.

As soon as the last subject had completed Part A of the protocol, the treatment groups were unblinded, and the results up to Week 17 were analyzed. As soon as the last subject has completed Part B of the protocol, results of study Weeks 26 and 38 will be analyzed.

Statistical methods

All statistical analyses performed for efficacy endpoints (non-inferiority) were based on the use of one-sided confidence intervals, using a 2.5% level of statistical significance. The per-protocol (PP) population was the population of primary interest for the efficacy analyses. All statistical hypothesis tests and confidence intervals performed for safety endpoints (superiority) were two sided, using a 5% level of statistical significance, using the safety population. As comparisons involve two dose levels, a Bonferroni correction for the hypothesis tests and confidence intervals was used. If the assumptions of any of the parametric analysis such as normality or variance heterogeneity were deemed invalid, then appropriate non-parametric methods were used instead.

The primary efficacy objective of demonstrating non inferior efficacy of PGL4001 versus GnRH-agonist to reduce excessive uterine bleeding was assessed by testing the null hypothesis that the difference in the percentage of subjects with PBAC < 75 at end-of-treatment visit (Week 13 visit) for PGL4001 minus GnRH agonist is equal to the non-inferiority margin of -20, versus the alternative hypothesis that the difference was greater than -20. Each PGL4001 treatment group was tested separately, with the confidence intervals produced using the Newcombe-Wilson score method (uncorrected). A successful outcome was deemed to occur if at least one of the 5mg or 10mg PGL4001 treatments resulted in a rejection of the null hypothesis.

The primary safety objective of demonstrating superior safety of PGL4001 versus GnRH-agonist with respect to serum E2 levels was assessed by testing the null hypothesis that there is no difference in the mean serum E2 levels at end of treatment visit (Week 13 visit) for PGL4001 compared with GnRH-agonist. The hypothesis was tested via a repeated measures analysis of covariance, after log transforming the data.

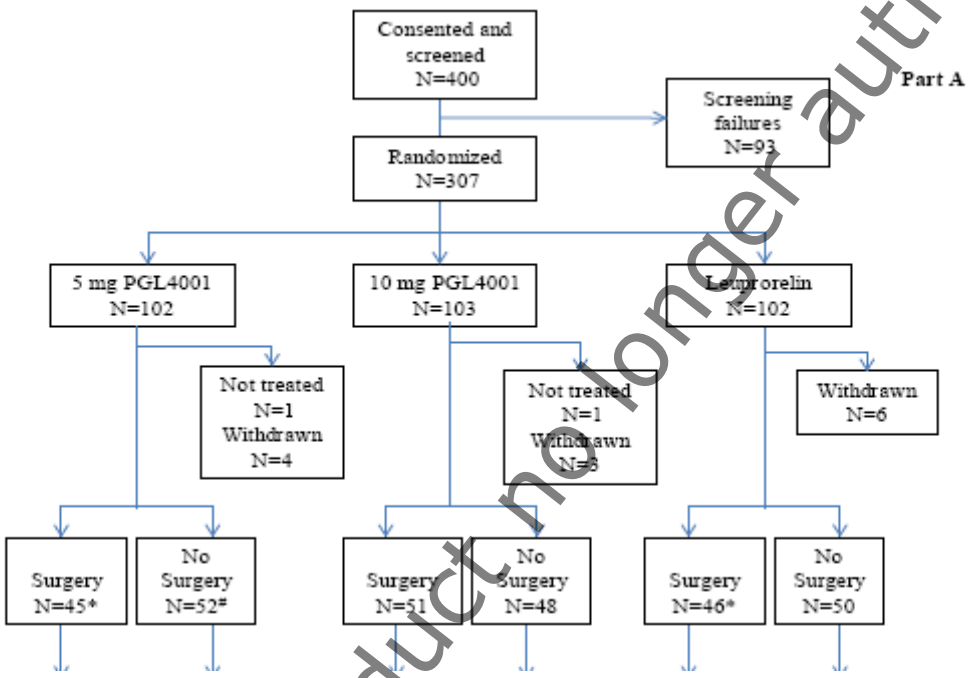
The primary safety objective of demonstrating superior safety of PGL4001 versus GnRH-agonist with respect to incidence of hot flushes was assessed by testing the null hypothesis that there is no difference in the percentage of subjects reporting moderate or severe hot flushes as adverse events throughout the treatment period for PGL4001 compared with GnRH-agonist. The hypothesis was tested

via a Cochran- Mantel-Haenszel test. A successful outcome was only deemed to occur if at least one of the 5mg or 10mg PGL4001 treatments resulted in a statistically significant improvement over GnRH-agonist with regards to both safety endpoints.

Results

Participant flow

Figure 4. Disposition of Subjects in Study PGL07-022 to week 17 (Part A)



Recruitment

The study period was from 18 August 2008 to 21 June 2010. This was a multinational study planned to be conducted in 30 sites. Thirty two sites actively recruited in 7 countries.

Conduct of the study

Individual major protocol deviations were reviewed in order to identify subjects who would need to be excluded from the PP population. If the reason a subject did not meet protocol compliance >80% was because of early withdrawal from the study then they would be excluded from the PP population, but that this was not a major protocol deviation. Subjects who stopped completing the PBAC before Week 8, or completed the PBAC retrospectively or for whom there was evidence that the subjects did not use the towels/tampons supplied for the study, would be excluded from the PP analysis.

A total of 14 subjects had at least one major protocol deviation, 6 (5.9%) subjects from the PGL4001 5 mg group, 4 (3.9%) subjects from the PGL4001 10 mg group and 4 (3.9%) subjects from the GnRH-agonist group. The table below provides a summary of the major protocol deviations in the subjects treated.

Table 17. Summary of Major Protocol Deviations (treated subjects)

Deviation Type	Treatment Group			Total (N=305)
	PGL4001 5mg (N=101)	PGL4001 10mg (N=102)	GnRH-agonist (N=102)	
At Least One Major Deviation	6 (5.9%)	4 (3.9%)	4 (3.9%)	14 (4.6%)
Inclusion / Exclusion Criteria	0	0	1 (1.0%)	1 (0.3%)
Received Incorrect Treatment Kit	2 (2.0%)	0	1 (1.0%)	3 (1.0%)
Treatment Compliance	0	1 (1.0%)	0	1 (0.3%)
Last non-missing on-treatment PBAC data is recorded on less than or equal to day 56	0	1 (1.0%)	0	1 (0.3%)
Screening PBAC data was completed retrospectively using different towels/tampons than those provided specifically for the study	0	1 (1.0%)	3 (2.9%)	4 (1.3%)
Prohibited Concomitant Medication	1 (1.0%)	0	0	1 (0.3%)
Other	4 (4.0%)	1 (1.0%)	1 (1.0%)	6 (2.0%)

Note: some subjects had more than one major protocol deviation

Source data: Table 14.1.6, Listing 16.2.2

Baseline data

The demographic characteristics of all randomized subjects for the Safety population by treatment received are presented in the table below. The characteristics were similar between treatment groups, and also between analysis populations. The majority of subjects in the study were of White origin (85.0%), and of childbearing potential (96.3%), where non-childbearing potential was defined as having undergone a tubal ligation prior to study start.

Table 18. Summary of demographic characteristics at baseline, safety population

Variable Parameter	Study PGL07-022			
	Leupro-relin (N=101)	Ulipristal acetate 5 mg/day (N=97)	Ulipristal acetate 10 mg/day (N=103)	Total (N=301)
Black	9 (8.9%)	9 (9.3%)	11 (10.7%)	29 (9.6%)
White	85 (84.2%)	83 (85.6%)	88 (85.4%)	256 (85.0%)
Asian	0	1 (1.0%)	1 (1.0%)	2 (0.7%)
Hispanic	5 (5.0%)	3 (3.1%)	2 (1.9%)	10 (3.3%)
Other	2 (2.0%)	1 (1.0%)	1 (1.0%)	4 (1.3%)
Age [years] (n)	101	97	103	301
Mean (SD)	40.3 (6.2)	40.1 (6.2)	40.7 (6.3)	40.4 (6.2)
Min/Max	24 / 51	25 / 50	20 / 50	20 / 51
Height [cm]	100	97	103	300
Mean (SD)	165.2 (5.9)	163.7 (6.4)	162.3 (6.7)	163.7 (6.4)
Min/Max	147 / 178	146 / 180	146 / 180	146 / 180
Weight [kg] (n)	100	97	103	300
Mean (SD)	67.9 (12.2)	68.3 (12.3)	68.8 (12.7)	68.4 (12.4)
Min/Max	48.0 / 119.0	48.5 / 108.0	46.0 / 111.0	46.0 / 119.0
BMI [kg/m2] (n)	100	97	103	300
Mean (SD)	24.9 (4.1)	25.4 (4.4)	26.2 (4.7)	25.5 (4.3)
Min/Max	18.4 / 39.3	19.4 / 37.8	18.1 / 39.8	18.1 / 39.8
Of Childbearing Potential N (%)	98 (97.0%)	93 (95.9%)	99 (96.1%)	290 (96.3%)

Numbers analysed

Efficacy analysis was conducted on both an intention-to-treat (ITT) population and a per protocol (PP) population although the PP population is the population of primary interest. 307 subjects were randomly assigned to one of 3 treatment groups: PGL4001 5 mg (N=102), PGL4001 10 mg (N=103) and GnRH-agonist (N=102). Two subjects were not treated due to inclusion error (N=1), subject request (N=1) and 4 were excluded from the analyses for GCP non compliance of the site.

The ITT population was defined as all randomized subjects who used the trial medication at least once, and who had post-baseline, that is, on-treatment, efficacy data for at least one efficacy endpoint. In the event that a subject received study medication other than that to which she was randomized, the analysis was to be performed using the treatment group to which she was randomized, rather than by the actual treatment she was administered. The ITT population was a subset of the Safety population

and consisted of 298 subjects: PGL4001 5 mg group (N=98), PGL4001 10 mg group(N=101) and GnRH-agonist group (N=99).

The PP population was a subset of the ITT population. Subjects who withdrew early from the study and as a consequence had a protocol compliance < 80% for either tablets or injections were excluded from the PP population. In addition, subjects with one or more major protocol deviations were excluded from the PP population. Protocol deviations including poor compliance occurring during Part A was determined before database lock at the end of Part A and un-blinding of the study. The PP population consisted of 281 subjects: PGL4001 5 mg group (N=93), PGL4001 10 mg group (N=95) andGnRH-agonist group (N=93).

All subjects who were randomized into the study and who used the trial medication at least once were considered evaluable for the safety population. In the event that a subject received study medication other than that to which she was randomized, the analysis was performed using the treatment actually received. A total of 301 subjects were included in the safety population: PGL4001 5 mg (N=97), PGL4001 10 mg (N=103) and GnRH-agonist (N=101).

Fifteen subjects discontinued the study prior to Week 17: 2 subjects were not treated and the remaining subjects discontinued due to study medication related AEs (N=5), unrelated AEs (N=3), subject request (N=2), lost to follow-up (N=1), non-compliance (N=1), and previous surgery (N=1).

Outcomes and estimation

Primary endpoints

Analysis of Uterine Bleeding: per protocol population

The analysis of the primary endpoint was the percentage of subjects with reduction of uterine bleeding at Week 13 visit defined as PBAC score <75 at end-of-treatment visit (Week 13 visit). The results are shown in the table below.

Table 19. Mean baseline PBAC scores and numbers of subjects with PBAC score < 75 at week 13 (Study PGL07-022, PP population, LOCF)

	Leuprorelin N = 93	Ulipristal acetate 5 mg/day N = 93	Ulipristal acetate 10 mg/day N = 95
PBAC at Baseline			
n	93	93	95
Mean PBAC score (SD)	404 (339)	379 (301)	328 (226)
Median PBAC score (min, max)	297 (102, 2104)	286 (109, 1984)	271 (120, 1809)
At Week 13			
n	92	93	95
Number (%) of Subjects with PBAC Score < 75	**82 (89.1%)**	**84 (90.3%)**	**93 (97.9%)**
Difference vs. control	-	1.2%	8.8%
2.5% LCL	-	**-9.3%**	**0.4%**

At baseline, a slightly higher mean and median PBAC score was observed in the leuprorelin group compared to the ulipristal treated, above all in the 10 mg group. The proportion of subjects with PBAC scores < 75 at week 13 was similar in both ulipristal acetate groups and in the leuprorelin group. Both

ulipristal treatment groups showed that the lower limit of the confidence interval was greater than the pre-specified non-inferiority margin of – 20% versus leuprorelin.

Analysis of Uterine Bleeding: pre-operative population

At Week 13, the proportion of pre-surgical subjects with PBAC < 75 was comparable between leuprorelin (89.6%), ulipristal acetate 5 mg (91.7%) and ulipristal acetate 10 mg (96.0%). The non-inferiority of both doses of ulipristal acetate to leuprorelin was demonstrated, with a 2.5% LCL (lower confidence limit) for the comparison between leuprorelin and ulipristal acetate of -12.7% and -6.7% for 5 mg and 10 mg respectively (pre-specified non-inferiority margin of -20%).

Secondary endpoints

The table below summarizes the key results of the secondary efficacy endpoints in the per-protocol population.

Table 20. Key results of secondary efficacy endpoints in Study PGL07-022, PP population

Parameter		PGL07-022 (PP Population)		
		Leuprorelin	Ulipristal acetate	
		N = 93	5 mg/day N = 93	10 mg/day N = 95
Median Change from Baseline in **PBAC** at Week 13[a]		-274	-268	-268
n (%) subjects in **Amenorrhea** at Week 13[a]		74 (80.4)	70 (75.3)	85 (89.5)
LS Mean Change from Baseline at Week 13 in:	**Hb** (g/dL)	0.5	0.5	0.6
	Hct (%)	1.6	1.6	2.0
	Ferritine (u/L)	2.8	2.2	8.1
n (%) subjects with **Hb >12 g/dL and Hct >36%**	Baseline	52 (57.8)	54 (59.3)	55 (59.8)
	Week 13[a]	71 (76.3)	71 (76.3)	73 (77.7)
LS Mean log_{10} change in **uterine volume**, Screening to Week 13		-0.25	**-0.08**	**-0.10**
n (%) with **Uterine volume** reduction ≥25%		-		
N (%) with **total fibroid volume** reduction ≥25%				
LS mean log_{10} change in **volume of 3 largest fibroids** from Screening to Week 13		-0.27	-0.18	-0.22
SF-MPQ median change from Baseline at Week 13[a]	Part A	-5.5	-5.0	-6.0
	Part B (VAS)	-32.0	-31.0	-32.5
	Part C (PPI)	-1.0	-1.0	-1.0
UFS-QoL LS mean change from baseline at Week 13[a]	Symptom Severity	-27.2	-28.2	-33.8
	HRQL Total Score	17.8	20.3	23.4
Measurement of Discomfort due to Uterine Fibroids Questionnaire, median change from Baseline, Week 13		-		

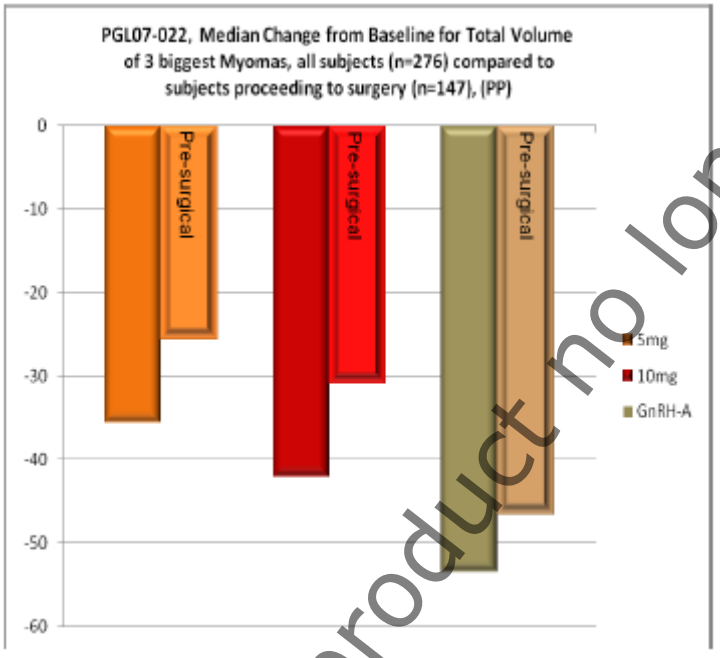
Bold values indicate that there was a significant difference between ulipristal acetate and leuprorelin. In study PGL07-022, the effects on the secondary endpoints were similar between the three treatment regimens except for a significantly larger reduction in the log 10 uterine volume from screening to Week 13 in leuprorelin treated women than subjects treated with either of the ulipristal doses.

Fibroid Size

The total volume of the three largest fibroids varied widely in all groups at both Screening (4.0 to 790.3 cm3 overall) and at Week 13 (0.7 to 735.4 cm3). The total volume of the three largest fibroids decreased in all groups from Screening to Week 13, and there were no statistically significant differences between groups (median percentage change of -53.5% with leuprorelin, and -35.6% and -42.1% with ulipristal acetate 5 and 10 mg respectively).

When analysing the pre-operative population (n= 142 subjects), the total volume of the three largest fibroids decreased by a similar amount across all groups from Screening to Week 13. The non-inferiority to leuprorelin was observed for the 5 mg group (median percentage change of -46.6% with leuprorelin, and -25.6% and -31.0% with ulipristal acetate 5 and 10 mg respectively, 2.5% LCL (lower confidence limit) for the comparison between leuprorelin and ulipristal acetate of -0.003% and 0.025% for 5 mg and 10 mg respectively. These results are illustrated in the Figure X below.

Figure 5. Median Change from Baseline for Total Volume of 3 biggest Myomas, PGL07-022



Improvement of Quality of Life

The UFS-QoL was used in all countries except Poland. Baseline mean (median) scores for the Symptom severity Score and the Health Related Quality of Life Score (HRQL Total Score) were comparable between treatment groups and between the overall study population and the pre-operative study population. All three treatment groups showed a marked mean (median) improvement compared to baseline in the UFS-QoL symptom severity score (decrease) and the HRQL total score (increase) which were in line with mean scores published for the UFS-QoL for patients with confirmed myoma (Baseline) and for healthy subjects (Week 13). For the symptom severity score, the median decrease ranged from -28.2 to -34.4 and for the HRQL total score the increase ranged from 20.7 to 26.7 between the three treatment groups. Comparing the overall population of Study PGL07-022 with the pre-operative population, no significant difference was observed. For the symptom severity score, the median decrease was very comparable to the overall population with a range from -28.1 to -34.4 between the three treatment groups. For the HRQL total score the increase ranged from 11.2 to 29.7 between the three treatment groups. This is illustrated in the Figures below.

Figure 6. Median Change from Baseline in Symptom Severity, PGL07-022

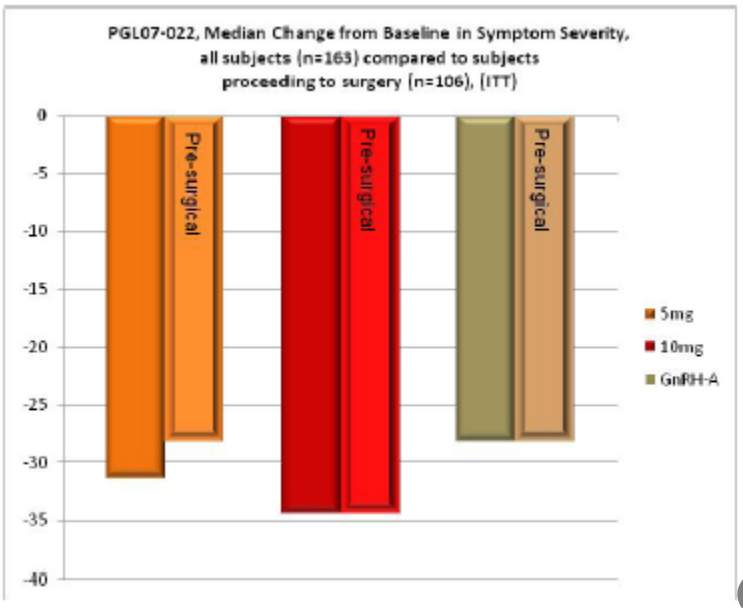
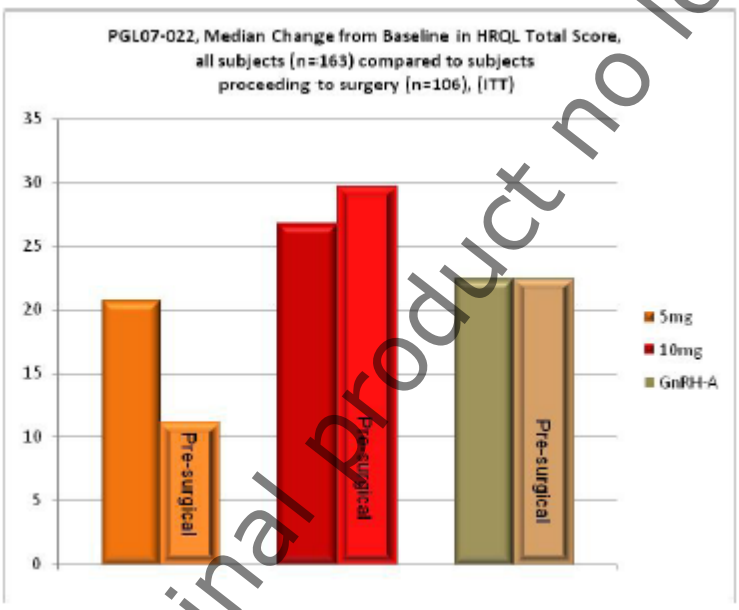


Figure 7. Median Change from Baseline in HRQL Total Score, PGL07-022



Improvement of Anaemia

Subjects were not required to have anaemia. However the mean (median) Hb values were similar for all three treatment groups at baseline (Range from 12.1 to 12.4 g/dl (12.5 to 12.6 g/dl). This was comparable to the pre-operative population (Range from 11.9 to 12.2 g/dl (12.1 to 12.4 g/dl)). In all three treatment groups Hb values increased over time without any important difference between the two study populations.

Ancillary analyses

Blood Transfusions

In the PP population, only 3 subjects had blood transfusions, and all occurred after the Week 13 visit due to surgery; 1 subject (PGL4001 5 mg group) received 450 mL of red blood cells, 1 subject (GnRH-agonist group) received 577 mL of concentrate and 1 subject (GnRHagonist group) received 500 mL of concentrate.

In the ITT population, a total of 5 subjects received transfusions. In addition to those for the PP population, 1 subject (PGL4001 5 mg group) received 547 mL concentrate after the Week 5 visit, and 1 subject (PGL4001 10 mg group) received 2 x 600 mL concentrate after the baseline visit due to SAE of worsening of uterine bleeding.

Proportion of subjects for whom surgery is cancelled because of improvement of symptoms, and proportion of subjects switched to less invasive surgery.

The distribution of planned surgeries was similar between the three treatment groups. Surgery was cancelled for about every second woman. Of those who underwent surgery, around 60% had a less invasive surgery than had been initially planned in all three treatment groups. After completion of Part B of the study, i.e. up to 6 months following the end of treatment, the cancellations of surgery were similar between all three treatment groups, i.e. 47%.

Table 21. Analysis of Surgery to week 17 (PP Population)

	Treatment Group		
	PGL4001 5mg (N=93)	PGL4001 10mg (N=95)	GnRH-agonist (N=93)
Missing	0	0	0
Non-Missing	93 (100.0%)	95 (100.0%)	93 (100.0%)
Surgery Cancelled (1)	52 (55.9%)	46 (48.4%)	50 (53.8%)
Difference	2.2%	-5.3%	
(PGL4001 - GnRH-agonist)~ 2.5% LCL (3)	~ -13.9%	~ -21.1%	
2.5% UCL (3)	18.0%	10.8%	
Planned and Completed not 'Other' (1)	92 (98.9%)	93 (97.9%)	93 (100.0%)
Less Invasive Surgery (2)	57 (62.0%)	56 (60.2%)	55 (59.1%)
Difference	2.8%	1.1%	
(PGL4001 - GnRH-agonist)~ 2.5% LCL (3)	~ -13.0%	~ -14.7%	
2.5% UCL (3)	18.4%	16.8%	

(1) Denominator for percentage is number of subjects with non-missing surgery information.
(2) Denominator for percentage is number of subjects with planned and completed surgery information non-missing and not 'Other'
(3) LCL = Lower confidence limit, UCL = Upper confidence limit; calculated using the Newcombe-Wilson score method (uncorrected); Bonferroni adjusted for multiplicity (two comparisons).

There was no relevant difference in the distribution of planned surgeries between the three treatment groups.

Fibroid size in patients who had not gone hysterectomy of myomectomy

An analysis was carried out on the subgroups of subjects who had not undergone hysterectomy or myomectomy during Week 13, to assess the change in fibroid size after the end of treatment, and at Weeks 17, 26 and 38 (using available data from Part B of the study).

A total of 135 subjects were included in the PP population for this analysis: 45 in the ulipristal acetate 5 mg/day group 46 in the ulipristal acetate 10 mg/day group and 44 in the leuprorelin group.

In the leuprorelin group, after Week 13 the mean total volume of the three largest fibroids increased rapidly. By Week 38 there was very little percentage change from Screening in total volume of the three largest fibroids (-3.1%).

With both doses of ulipristal acetate the increases in fibroid size after the end of treatment were small, and the reduction in total volume of the three largest fibroids seen on-treatment was well maintained up to 6 months after the end of treatment. With ulipristal acetate 5 mg/day, the mean % decrease in total volume of the three largest fibroids was very similar at Weeks 13 and 38 (-37.3% and -38.8% respectively). The higher dose of ulipristal acetate showed a greater decrease in fibroid volume on-treatment (Week 13: -54.2%), but by Week 38 the % change from Screening with ulipristal acetate 10 mg/day (-30.0%) was similar to that of ulipristal acetate 5 mg/day.

Return of menstruation

In the placebo 82% had return to menstruation at week 17. The corresponding figures for ulipristal acetate 5 mg and 10 mg was 72% and 66%, respectively. In the ulipristal groups the median time for menstruation return was about one week later than with the placebo, and within on month after end of treatment. In the GnRH-agonist group 29% had return to menstruation at week 17. The corresponding figures for ulipristal acetate 5 mg and 10 mg was 64% and 65% respectively. In ulipristal acetate as well as GnRH-agonist the mean and median time for menstruation return was about three weeks.

Summary of main studies

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 22: Summary of Efficacy for trial *PGL07-021*

Results and Analysis				
Analysis description	**Primary Analysis**			
Analysis population and time point description	Intent to treat population at Week 13			
Descriptive statistics and estimate variability	Treatment group	PGL4001 5mg	PGL4001 10mg	Placebo
	Number of subject	96	98	48
	PBAC Score <75	91.5%	92.5%	18.8%
	Variability statistic	n/a	n/a	n/a

	Percentage change in Total myoma volume: Median	-21.2	-12.3	3.00
	Variability statistic (min, max)	-100.0, 223.4	-100.0, 146.6	-100.0, 134.8

Effect estimate per comparison	Analysis of PBAC	Comparison groups	PGL4001 5mg vs. Placebo
		% Difference	72.7%
		95% CI	(55.1%, 83.2%)
		P-value	<0.001
	Analysis of PBAC	Comparison groups	PGL4001 10mg vs. Placebo
		% Difference	73.7%
		95% CI	(56.2%, 84.0%)
		P-value	<0.001
	Total Myoma volume	Comparison groups	Placebo vs. PGL4001 5mg
		Median difference	-22.6
		95% CI	(-36.1, -8.20)
		P-value	0.002
	Total Myoma volume	Comparison groups	Placebo vs. PGL4001 10mg
		Median difference	-18.2
		95% CI	(-33.0, -5.2)
		P-value	0.006
Notes			
Analysis description	**Total Myoma Volume**		
	Hodges-Lehmann point estimator used for the difference between groups, with the corresponding Moses confidence interval (Bonferroni adjusted for multiplicity (two comparisons))		

Table 23: Summary of Efficacy for trial *PGL07-022*

Results and Analysis				
Analysis description	**Primary Analysis**			
Analysis population and time point description	Per protocol population at Week 13			
Descriptive statistics and estimate variability	Treatment group	PGL4001 5mg	PGL4001 10mg	GnRH-agonist Leuprorelin
	Number of subject	102	103	102
	PBAC Score <75	90.3%	97.9%	89.1%
	Variability statistic>	n/a	n/a	n/a

	% change from screening to week 13 in the three largest myomas by ultrasound Mean myoma volume	-27.4	-36.7	-42.0
	Standard Deviation	51.2	43.1	70.2
	% change from screening to week 13 in the three largest myomas by ultrasound Median myoma volume	-35.5	-42.1	-53.5
	(min, max)	-98.0, 230.8	-95.5.0, 120.0	-91.0.0, 527.7

Effect estimate per comparison	Analysis of PBAC	Comparison groups	PGL4001 5mg vs. GnRH-agonist
		% Difference	1.2%
		2% Lower Confidence Limit	-9.3%
		P-value	n/a
	Analysis of PBAC	Comparison groups	PGL4001 10mg vs. GnRH-agonist
		% Difference	8.8%
		2% Lower Confidence Limit	0.4%
		P-value	n/a
	Total Myoma volume of the three largest fibroids assessed by ultrasound	Comparison groups	PGL4001 5mg vs. Leuprorelin
		Log 10 change from screening Mean difference	0.09
		2.5% LCL	-0.003
		2.5% UCL	0.181
	Total Myoma volume of the three largest fibroids assessed by ultrasound	Comparison groups	PGL4001 10mg vs. Leuprorelin
		Log 10 change from screening Median difference	0.05
		2.5% LCL	-0.043
		2.5% UCL	0.140
Notes			
Analysis description			

	All statistical analyses performed for efficacy endpoints (non-inferiority) were based on the use of one-sided confidence intervals using a 2.5% level of statistical significance. The Per-protocol population was the population of primary interest for the efficacy analyses.

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

No analyses performed across trials were submitted.

Clinical studies in special populations

No clinical studies in special populations were submitted.

Supportive study(ies)

No supportive studies were submitted.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The primary goal of the ulipristal treatment in the pivotal studies was to reduce heavy menstrual bleeding and anaemia, decrease myoma related symptoms prior to surgery.. The inclusion and exclusion criteria for the pivotal studies are considered acceptable. The primary and secondary as well as exploratory objectives in study PGL07-021 and PGL07-022 are considered adequate. The study populations were considered acceptable.

Patients could discriminate between menorraghia and normal menstrual blood loss using PBAC. Ultrasound or MRI was used for measurement of fibroid and uterus volumes.

Efficacy data and additional analyses

For treatment of fibroid related bleeding and anaemia, ulipristal acetate was superior compared to placebo after 3 months of treatment (PGL07-021) and non-inferior to a GnRH-agonist (PGL07-022). Sensitivity analyses have been performed supporting a statistically significant difference in favour of ulipristal acetate vs placebo regarding both co-primary endpoints PBAC score and percent change in total myoma volume in study.

There was a significantly greater decrease in discomfort in the ulipristal acetate treatment groups compared to placebo. However, all three treatment groups showed an improvement for the ITT population. With regard to pain, a greater reduction but no statistically significant difference was seen between ulipristal acetate 5 mg and placebo.

With regards to fibroid volume reduction, a statistically significant higher efficacy compared to placebo was found. In comparison to GnRH-agonist treatment, ulipristal acetate, although not statistically significant, showed statistically non-inferior efficacy on fibroid volume.

A responder analysis regarding the reduction of the three largest myomas and reduction of uterine volume for Study PGL07-022 was submitted. In the analysis, ulipristal acetate 5 mg was inferior to leuprorelin with regards to the proportion of subjects with a ≥25% decrease in total volume of the

three largest myomas (at week 13: 76% for ulipristal acetate 5 mg, 87% for ulipristal acetate 10 mg and 86% for leuprorelin).

Regarding uterine volume reduction, both the ulipristal doses were inferior compared to leuprorelin (at week 13: 57% for ulipristal acetate 5 mg, 50% for ulipristal acetate 10 mg and 91% for leuprorelin).

The difference in pharmacological effect of ulipristal acetate and leuprorelin, regarding reduction of the myoma and uterine volume may be of importance for choice of preoperative treatment. However, a positive effect on surgical performance has still to be proven as it was not demonstrated in the submitted studies (studies not powered to that effect).

Another aspect is whether the treatment could be used in order to postpone or even avoid surgery. Such an effect would be beneficial for perimenopausal women suffering from heavy uterine bleeding and other fibroid related symptoms. Not all women were obliged to have surgery in the pivotal phase III trials and it is therefore not unexpected that the cancellation rate for surgery was high in all treatment groups.

In clinical practice, the interaction between the treating physician and the patient has major impact on whether the patient decides to have surgery. Data indicate for Study PGL07-021 that the site (investigator and his/her team) appears an important factor in determining whether the patient eventually progresses with the previously discussed surgery as in some centers practically all patients underwent surgery and in other almost none.

The applicant has submitted data for the pivotal trials corresponding to 1-6 months after discontinuation of treatments, which includes all surgeries up to 6 months post-treatment. In the active-comparator study versus GnRH-agonist, the proportion of patients not proceeding to surgery was the same for all treatment groups, i.e. 47%.

For the placebo-controlled study, the data from the double-blind 3 month treatment and 1 month follow-up initially raised concern, as the highest cancellation of surgery was present in the placebo group (73%). It is reassuring that when the data from the discontinuation phase are also taken into account for the placebo-controlled study, the cancellation of surgery for the placebo group and the 5 mg ulipristal acetate group is very similar, i.e. 58% and 56%, respectively.

Further, in the 10 mg ulipristal acetate group the proportion of women not proceeding to surgery was slightly lower (46%), though comparable with all treatment groups in the active comparator controlled trial (47%).

Sub-analyses showed that the women who had surgery and those who did not have surgery were comparable at baseline for severity of menstrual bleeding and pain. Only the total myoma volume tended to be greater in women who progressed to surgery, but the myoma volume was very wide in all treatment groups, and could not be retrospectively used for prediction if a woman would have surgery or not.

The effects of a 3-month course of ulipristal acetate will not only last the 3 months of treatment, but also continue to have benefits for the patients after stopping with Esmya. The reduction in bleeding or amenorrhoea achieved during treatment is sustained to up to 1 month after discontinuation. In the

subgroup of patients where surgery was cancelled, the decrease in fibroid size seems better maintained with ulipristal acetate than after GnRH-agonist treatment in the comparator-controlled trial.

To gather additional information on the impact of ulipristal acetate treatment on surgery, the applicant will follow-up subjects with uterine fibroids in the practice of targeted prescribers, as part of a non-interventional study (PGL10-014) and as part of a prescription patters/drug utilization study (PGL11-020) (included in the RMP).

2.5.4. Conclusions on the clinical efficacy

The clinical efficacy of Esmya in the current indication has been adequately justified. To gather additional information on the impact of ulipristal acetate treatment on surgery, the applicant will follow-up subjects with uterine fibroids in the practice of targeted prescribers, as part of a non-interventional study (PGL10-014) and as part of a prescription patters/drug utilization study (PGL11-020). These post-authorisation measures are adequately covered in the RMP.

2.6. Clinical safety

Clinical safety data has been submitted for 4 randomized, double-blind, repeated-dose studies carried out in the target population, and from 17 studies in healthy female subjects/subjects requiring emergency contraception (2 repeated-dose and 15 single-dose studies).

Patient exposure

Of the 5323 subjects who have been exposed to ulipristal acetate during its clinical development, a total of 498 subjects received repeated doses of ulipristal acetate. Four hundred eighty six subjects received repeated doses of 5 mg/day or higher (419 were exposed for ≥12 weeks). In addition, 4825 subjects have received a single dose of ulipristal acetate, of whom 4819 received 5 mg/day or higher. The safety database includes 439 women with symptomatic uterine fibroids from Studies PGL-0287, PGL-N-0090, PGL07-021 and PGL07-022.

In addition, Phase III ongoing Study PGL09-026 interim safety analysis provides data on 124 patients treated for symptomatic uterine fibroids of which 110 were treated for at least 12 weeks with ulipristal acetate 10 mg is available (cut-off date 15 March 2011).
In total, 529 subjects or patients were exposed to 3 months treatment ulipristal acetate to the target dose of 5 mg or above.

Adverse events

Based on pooled data from two phase III studies in patients with uterine fibroids treated for 3 months, the following adverse reactions have been reported (see table below).

Table 24. Tabulated list of adverse reactions

MedDRA	Adverse reactions		
System Organ Class	**Very common**	**Common**	**Uncommon**
Psychiatric disorders		Emotional disorder	Anxiety
Nervous system disorders		Headache	Dizziness
Ear and labyrinth disorders		Vertigo	
Respiratory, thoracic and mediastinal disorders			Epistaxis
Gastrointestinal disorders		Abdominal pain Nausea	Dyspepsia Dry mouth Flatulence Constipation
Skin and subcutaneous tissue disorders		Acne Hyperhidrosis	Skin lesion
Musculoskeletal and connective tissue disorders		Musculoskeletal pain	Back pain
Renal and urinary disorders			Urinary incontinence
Reproductive system and breast disorders	Amenorrhea Endometrial thickening Hot flush	Uterine haemorrhage Ovarian cyst Breast tenderness/pain Pelvic pain	Metrorrhagia Ovarian cyst ruptured Genital discharge Breast swelling Breast discomfort
General disorders and administration site conditions		Oedema Fatigue	Asthenia
Investigations		Blood cholesterol increased	Blood triglycerides increased Weight increased

Study PGL07-021

The safety objectives of Study PGL07-021 were to assess overall safety of ulipristal acetate (PGL4001) in subjects with uterine myomas. A general summary of the adverse events recorded in Part A of the study, in the safety population, is provided in the table below.

Table 25. General Summary of Adverse Events Part A (Safety Population)

	Treatment Group								
	Placebo (N=48)			PGL4001 5 mg (N=95)			PGL4001 10 mg (N=98)		
	n	N	(%)	n	N	(%)	n	N	(%)
At Least One Adverse Event	53	24	50.0	102	48	50.5	121	52	53.1
At Least One TEAE	47	22	45.8	90	47	49.5	113	52	53.1
At Least One Severe TEAE	3	3	6.3	4	3	3.2	1	1	1.0
At Least One Study Medication Related TEAE	8	4	8.3	30	18	18.9	34	22	22.4
At Least One Serious TEAE	2	2	4.2	2	2	2.1	1	1	1.0
At Least One Serious Study Medication Related TEAE	0	0		0	0		0	0	
TEAE With Action Taken Study Drug Discontinued	1	1	2.1	1	1	1.1	1	1	1.0
TEAE Leading to Study Withdrawal	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).

TEAE: Treatment emergent adverse events (Part A) are defined as events whose start date is on or after the first dose of study drug and on or before the last assessment date of visit 6 (Week 17).

The frequency of AEs was similar across the treatment groups. The proportion of subjects reporting at least one study medication related treatment emergent adverse events (TEAEs) was about 22.4-18.9% in the ulipristal acetate groups compared to 8.3% in the placebo group in Study PGL07-021.

Table 26. Summary of Treatment Emergent Adverse Events Occurring in ≥3% of the Subjects in any Treatment Group Presented by System Organ Class and Preferred Term Part A (Safety Population) in Study PGL07-021

System Organ Class/ Preferred Term	Treatment Group								
	Placebo (N=48)			PGL4001 5 mg (N=95)			PGL4001 10 mg (N=98)		
	n	N	%	n	N	%	n	N	%
At least one TEAE	47	22	45.8	90	47	49.5	113	52	53.1
Reproductive system and breast disorders	**10**	**6**	**12.5**	**18**	**14**	**14.7**	**16**	**14**	**14.3**
Breast pain / tenderness / discomfort	0	0	0.0	2	2	2.1	6	6	6.1
Dysmenorrhea	3	2	4.2	0	0	0.0	0	0	0.0
Gastrointestinal disorders	**7**	**3**	**6.3**	**16**	**9**	**9.5**	**13**	**10**	**10.2**
Abdominal pain	2	2	4.2	3	2	2.1	5	3	3.1
Constipation	1	1	2.1	6	4	4.2	0	0	0.0
Nervous system disorders	**4**	**3**	**6.3**	**7**	**4**	**4.2**	**22**	**11**	**11.2**
Headache	2	2	4.2	6	4	4.2	19	10	10.2
Dizziness	0	0	0.0	1	1	1.1	3	3	3.1
Infections and infestations	**4**	**3**	**6.3**	**8**	**8**	**8.4**	**15**	**12**	**12.2**
Influenza	1	1	2.1	1	1	1.1	3	3	3.1
Nasopharyngitis	0	0	0.0	3	3	3.2	0	0	0.0
Endocrine disorders	**2**	**1**	**2.1**	**8**	**5**	**5.3**	**8**	**8**	**8.2**
Hypothyroidism	0	0	0.0	2	2	2.1	4	4	4.1
Metabolism and nutrition disorders	**3**	**2**	**4.2**	**10**	**7**	**7.4**	**4**	**4**	**4.1**
Hypercholesterolemia	1	1	2.1	4	3	3.2	2	2	2.0
General disorders and administration site conditions	**3**	**2**	**4.2**	**5**	**5**	**5.3**	**4**	**4**	**4.1**
Pyrexia	2	2	4.2	3	3	3.2	2	2	2.0

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

TEAE: Treatment emergent adverse events (Part A) are defined as events whose start date is on or after the first dose of study drug and on or before the last assessment date of visit 6 (week 17) (all causality, i.e. assessed as related and not related by investigators).

Headache was reported by 4.2% of subjects in the placebo group, 4.2% of subjects in the PGL4001 5 mg group and 10.2% of subjects in the PGL4001 10 mg group. None of the events of headache were reported as severe. Three 3 cases of weight increase or obesity were reported among the 193 ulipristal acetate (PGL4001) treated subjects. A comparison of on-treatment AEs with those observed up to Week 17 revealed a similar distribution of AEs.

In this study, the majority of TEAEs were assessed as mild or moderate for all treatment groups. A total of 8 TEAEs were assessed as severe; no pattern in occurrence could be identified. No subjects withdrew from the study due to TEAEs. There were no deaths during the study.

ECG

Three subjects in Study PGL07-021 had cardiac disorders reported as TEAEs during the study; all of them were reported as being of mild severity. No action was taken and no treatment was given and all three events resolved spontaneously.

One subject, in the PGL4001 5 mg group, had a single episode of sinus bradycardia reported on her last day of study medication; at this time point her pulse rate was 60 beats/min, a change from baseline of -22 beats/min. The investigator considered this event to be related to study medication.

One subject, in the PGL4001 10 mg group, had a single episode of sinus arrhythmia reported 4 days after receiving her last dose of study medication. The investigator considered this event to be unrelated to study medication.

Another subject in the PGL4001 10 mg group, had a recurrent episode of angina pectoris reported whilst she was on the second month of treatment. Her ECG and physical examination were normal at baseline; there was no history of cardiovascular disease. The investigator considered this event to be unrelated to study medication.

Endometrium Thickness (assessed by MRI and week 13 of all subjects)

The distribution of endometrium thickness at the screening visit was comparable between each treatment group, with a median of 7.0 mm for all groups, and an overall range between 2.0 mm and 19.4 mm. At Week 13 the median endometrium thickness was 8.10 mm, 6.30 mm and 7.05 mm in the placebo, 5 mg and 10 mg ulipristal acetate groups, respectively

Table X: Analysis of endometrium thickness at screening and week 13 (safety population)

Endometrial Thickness (mm)		Placebo (N= 48)	Ulipristal acetate	
			5 mg/day (N = 95)	10 mg/day (N = 98)
Screening	≤ 4 mm, n (%)	5 (10.4)	19 (20.0)	12 (12.2)
	> 16 mm, n (%)	0	1 (1.1)	2 (2.0)
	Mean (SD)	**8.25 (3.51)**	**6.77 (3.05)**	**7.89 (3.33)**
Week 13[a]	≤ 4 mm, n (%)	5 (10.4)	14 (14.7)	16 (16.3)
	> 16 mm, n (%)	1 (2.1)	10 (10.5)	7 (7.1)
	LS Mean (SE)	**8.22 (0.80)**	**8.66 (0.61)**	**8.46 (0.61)**
	Difference	-	0.45	0.24
	95% CI		1.68, 2.58	-1.89, 2.38

In Study PGL07-021, the MRI measurement at week 13 revealed more subjects in the ulipristal acetate groups with endometrium thickness >16 mm at week 13 (end of treatment).

Endometrium Thickness Assessed by MRI at screening and up to week 38 follow up (subjects without hysterectomy or endometrial ablation)

The distribution of endometrium thickness at screening, end of treatment at week 13, and the week 26 and 38 follow up visits are given in the table below for patients who did not have hysterectomy or endometrial ablation.

Table 27. Summary of Endometrium Thickness (subjects without hysterectomy or endometrial ablation)

		Treatment Group			
	Value (mm)	Placebo (N=48)	PGL4001 5mg (N=95)	PGL4001 10mg (N=98)	Total (N=241)
Completed Part A	Yes	45	89	90	224
Hysterectomy or Myomectomy Performed	Yes	15	29	33	77
	No	30	60	57	147
Screening	N	30	59	55	144
	Mean	7.9	6.9	7.9	7.5
	SD	3.2	3.4	3.2	3.3
	Median	**8.0**	**6.3**	**7.2**	**6.7**
	Min, Max	3, 16	3, 19	3, 15	3, 19
	<=4 mm	4 (13.3%)	13 (21.7%)	7 (12.3%)	24 (16.3%)
	>4 to <=16 mm	26 (86.7%)	45 (75.0%)	48 (84.2%)	119 (81.0%)
	>16 mm	0	1 (1.7%)	0	1 (0.7%)
	Missing	0	1 (1.7%)	2 (3.5%)	3 (2.0%)
Week 13	N	30	58	55	143
	Mean	8.7	8.4	8.2	8.4
	SD	3.5	5.7	5.0	5.0
	Median	**8.5**	**6.5**	**7.0**	**7.1**
	Min, Max	2, 17	2, 28	2, 25	2, 28
	<=4 mm	3 (10.0%)	11 (18.3%)	11 (19.3%)	25 (17.0%)
	>4 to <=16 mm	26 (86.7%)	41 (68.3%)	40 (70.2%)	107 (72.8%)
	>16 mm	1 (3.3%)	6 (10.0%)	4 (7.0%)	11 (7.5%)
	Missing	0	2 (3.3%)	2 (3.5%)	4 (2.7%)
Week 26	N	28	56	55	139
	Mean	7.6	7.1	7.1	7.2
	SD	3.3	4.0	5.0	4.2
	Median	**6.8**	**6.1**	**5.2**	**6.3**
	Min, Max	3, 15	3, 20	2, 33	2, 33
	<=4 mm	3 (10.0%)	13 (21.7%)	13 (22.8%)	29 (19.7%)
	>4 to <=16 mm	25 (83.3%)	40 (66.7%)	39 (68.4%)	104 (70.7%)
	>16 mm	0	3 (5.0%)	3 (5.3%)	6 (4.1%)
	Missing	2 (6.7%)	4 (6.7%)	2 (3.5%)	8 (5.4%)
Week 38	N	28	49	53	130
	Mean	7.8	6.8	7.2	7.2
	SD	4.2	3.8	3.2	3.7
	Median	**6.8**	**5.9**	**6.3**	**6.1**
	Min, Max	3, 20	2, 22	3, 17	2, 22
	<=4 mm	6 (20.0%)	10 (16.7%)	5 (8.8%)	21 (14.3%)
	>4 to <=16 mm	21 (70.0%)	37 (61.7%)	47 (82.5%)	105 (71.4%)
	>16 mm	1 (3.3%)	2 (3.3%)	1 (1.8%)	4 (2.7%)
	Missing	2 (6.7%)	11 (18.3%)	4 (7.0%)	17 (11.6%)

Summary only includes subjects who completed Part A and where no hysterectomy or myomectomy was performed prior to Visit 8 (Week 38).
Source: Table 14.3.34.1

At Week 38, the median endometrium thicknesses for all groups were slightly lower than at screening: 6.8 mm, 5.9 mm and 6.3 mm for the Placebo, PGL4001 5 mg and 10 mg groups, respectively. The proportion of subjects with endometrium thickness > 16 mm was similar across treatment groups, 1 (3.3%) subject, 2 (3.3%) subjects and 1 (1.8%) subject from the three groups, respectively.

Endometrium Biopsy (Diagnosis) from screening up to Week 13 for all subjects, using pre-defined histological classification.

Endometrium samples were collected and assessed by three independent pathologists who were blinded to treatment allocation, visit sequence in the study and to each other's assessment. A summary of endometrium biopsy consensus between the three pathologists at screening and Week 13 is presented in the table below for all subjects. The results of the histological examination of the endometrium showed no hyperplasia or cancer at Week 13. One hyperplastic polyp was diagnosed in the 10 mg ulipristal acetate group at Week 13.

Table 28. Summary of Endometrium Biopsy Consensus at screening and week 13 (Study PGL07-021 Safety Population)

Visit	Category	Major Class / subclass	Treatment Group		
			Placebo (N=48)	PGL4001 5mg (N=95)	PGL4001 10mg (N=98)
Screening	Specimen adequate (1)	No	0	0	0
		Yes	48 (100.0%)	88 (92.6%)	95 (96.9%)
	Primary diagnosis (2)	Benign:			
		Benign endometrium	48 (100.0%)	87 (91.6%)	95 (96.9%)
		Hyperplasia:	0	1 (1.1%)	0
		Simple, non-atypical	*0*	*0*	*0*
		Complex, non-atypical	*0*	*0*	*0*
		Simple, atypical	*0*	*0*	*0*
		Complex, atypical	*0*	*1 (1.1%)*	*0*
		Malignant neoplasm:	0	0	0
		Endometrial adenocarcinoma	0	0	0
		Other malignant neoplasm	0	0	0
	Observation (2)	Polyps:			
		Absent	48 (100.0%)	88 (92.6%)	95 (96.9%)
		Present: benign	0	0	0
		Present: hyperplasic	0	0	0
		Present: carcinomatous	0	0	0
Week 13	Specimen adequate (1)	No	2 (4.2%)	5 (5.3%)	3 (3.1%)
		Yes	39 (81.3%)	78 (82.1%)	78 (79.6%)
	Primary diagnosis (2)	Benign:			
		Benign endometrium	39 (81.3%)	78 (82.1%)	78 (79.6%)
		Hyperplasia:	0	0	0
		Simple, non-atypical	*0*	*0*	*0*
		Complex, non-atypical	*0*	*0*	*0*
		Simple, atypical	*0*	*0*	*0*
		Complex, atypical	*0*	*0*	*0*
		Malignant neoplasm:	0	0	0
		Endometrial adenocarcinoma	0	0	0
		Other malignant neoplasm	0	0	0
	Observation (2)	Polyps:			
		Absent	39 (81.3%)	77 (81.1%)	77 (78.6%)
		Present: benign	0	1 (1.1%)	0
		Present: hyperplasic	0	0	1 (1.0%)
		Present: carcinomatous	0	0	0

Note: Table shows consensus results from the three independent pathologists. (1) Yes = At least one assessor deemed specimen adequate,
No = Otherwise. (2) Of those who deem specimen adequate, at least two assessors have the same opinion; otherwise the most severe is used.
Denominator of percentage is the number of subjects in the treatment group.

Endometrium Biopsy (Diagnosis) from screening up to week 38 follow up visit (subjects without hysterectomy or endometrial ablation), using pre-defined histological classification.

The results presented below for all time points are only for those subjects who did not undergo hysterectomy or endometrial ablation. All subjects were diagnosed with benign endometrium at all time points, except one subject in the 5 mg ulipristal acetate group who was diagnosed with complex, atypical hyperplasia at screening, and one subject in the placebo group who was diagnosed with complex, atypical hyperplasia at Week 38. Polyps were not diagnosed in any subjects at screening, in one subject at Week 13 (PGL4001 5 mg group) and in another subject at Week 38 (PGL4001 5 mg group). There was no diagnosis of malignant neoplasms at any time point.

Table 29. Summary of Endometrium Biopsy Consensus at screening, week 13 and week 38 follow up visit

			Treatment Group			
Visit	**Category**	**Major Class Subclass**	**Placebo (N=48)**	**PGL4001 5mg (N=95)**	**PGL4001 10mg (N=98)**	**Total (N=241)**
Hysterectomy or Endometrium Ablation Performed		Yes	10	18	20	48
		No	38	77	78	193
Screening	Specimen Adequate (1)	No	0	0	0	0
		Yes	38 (100.0%)	72 (93.5%)	76 (97.4%)	186 (96.4%)
	Primary Diagnosis (2)	Benign Endometrium	38 (100.0%)	71 (92.2%)	76 (97.4%)	185 (95.9%)
		Hyperplasia:	0	1 (1.3%)	0	1 (0.5%)
		Complex, Atypical	0	1 (1.3%)	0	1 (0.5%)
	Observation (2)	Polyps:				
		Absent	38 (100.0%)	72 (93.5%)	76 (97.4%)	186 (96.4%)
		Present: Benign	0	0	0	0
Week 13	Specimen	No	1 (2.6%)	5 (6.5%)	0	6 (3.1%)
	Adequate (1)	Yes	31 (81.6%)	62 (80.5%)	63 (80.8%)	156 (80.8%)
	Primary Diagnosis (2)	Benign Endometrium	31 (81.6%)	62 (80.5%)	63 (80.8%)	156 (80.8%)
		Hyperplasia	0	0	0	0
	Observation (2)	Polyps:				
		Absent	31 (81.6%)	61 (79.2%)	63 (80.8%)	155 (80.3%)
		Present: Benign	0	1 (1.3%)	0	1 (0.5%)
Week 38	Specimen Adequate (1)	No	1 (2.6%)	3 (3.9%)	2 (2.6%)	6 (3.1%)
		Yes	30 (78.9%)	60 (77.9%)	61 (78.2%)	151 (78.2%)
	Primary Diagnosis (2)	Benign Endometrium	29 (76.3%)	60 (77.9%)	61 (78.2%)	150 (77.7%)
		Hyperplasia:	1 (2.6%)	0	0	1 (0.5%)
		Complex, Atypical	1 (2.6%)	0	0	1 (0.5%)
	Observation (2)	Polyps:				
		Absent	30 (78.9%)	59 (76.6%)	61 (78.2%)	150 (77.7%)
		Present: Benign	0	1 (1.3%)	0	1 (0.5%)

Note: Summaries only include subjects where no hysterectomy or endometrium ablation was performed prior to Visit 8 (Week 38).
Denominator of percentage is the number of subjects where no hysterectomy or endometrium ablation was performed.
Table shows consensus results from the three independent pathologists. (1) Yes = At least one assessor deemed specimen adequate, No = Otherwise. (2) Of those who deem specimen adequate, at least two assessors have the same opinion; otherwise the most severe is used.

Endometrium Biopsy Non-Physiological Descriptions (PAEC)

In the safety population at Week 13, the numbers of subjects with endometrium biopsies for which all three pathologists reported “non-physiological” changes in the endometrium was no case (0.0%) in the placebo group, and 32 (41.6%) cases and 29 (37.2%) cases in the PGL4001 5 mg and 10 mg groups, respectively. The transformation was associated with a significant reduction in proliferative endometrium.

The subjects treated with ulipristal acetate had findings of non-physiological endometrium with a similar incidence between the two treatment groups at week 13. Above all were epithelial changes present in the ulipristal groups.

Of the 193 subjects who did not have hysterectomy or endometrial ablation, a large proportion gave adequate specimens at screening 186 (96%) subjects, at Week 13, 162 (84%) subjects and at Week 38, 149 (80%) subjects. The non-physiological changes seen on treatment were generally reversible. At Week 38 only 1 (1.3%) subject from the 5 mg ulipristal acetate group and 3 (3.8%) subjects from the 10 mg ulipristal acetate group had the diagnosis of non-physiological changes by all 3 pathologists. When reviewing concurrent assessment of 2 or 3 pathologists, non-physiological changes were observed for 1 (2.6%) subject, 6 (7.8%) subjects and 4 (5.1%) subjects from the Placebo, 5 mg and 10 mg ulipristal acetate groups, respectively. The incidence of non-physiological Progesterone Receptor Modulator associated endometrial changes (PAEC) at week 38 (6 months after end of treatment) was similar to that observed at screening.

There was a wide variation in the histopathologic evaluation of the endometrial specimens.

Table 30. Summary of Endometrium Biopsy Non-Physiological Descriptions (PAEC) from screening up to Week 38 follow up visit.

			Treatment Group			
Visit	**Description**	**Number of Pathologists who observed Description**	**Placebo (N=48)**	**PGL4001 5mg (N=95)**	**PGL4001 10mg (N=98)**	**Total (N=241)**
Hysterectomy or Endometrium Ablation Performed		Yes	10	18	20	48
		No	38	77	78	193
Screening	**Non-physiological**	**None**	**31 (81.6%)**	**56 (72.7%)**	**58 (74.4%)**	**145 (75.1%)**
		1	**7 (18.4%)**	**11 (14.3%)**	**17 (21.8%)**	**35 (18.1%)**
		2	**0**	**5 (6.5%)**	**1 (1.3%)**	**6 (3.1%)**
		3	**0**	**0**	**0**	**0**
	Epithelial changes present	*None*	*32 (84.2%)*	*57 (74.0%)*	*59 (75.6%)*	*148 (76.7%)*
		1	*6 (15.8%)*	*11 (14.3%)*	*16 (20.5%)*	*33 (17.1%)*
		2	*0*	*4 (5.2%)*	*1 (1.3%)*	*5 (2.6%)*
		3	*0*	*0*	*0*	*0*
	Extensive cyst formation	*None*	*38 (100.0%)*	*71 (92.2%)*	*76 (97.4%)*	*185 (95.9%)*
		1	*0*	*1 (1.3%)*	*0*	*1 (0.5%)*
		2	*0*	*0*	*0*	*0*
		3	*0*	*0*	*0*	*0*
	Unusual vascular changes present	*None*	*33 (86.8%)*	*58 (75.3%)*	*63 (80.8%)*	*154 (79.8%)*
		1	*5 (13.2%)*	*11 (14.3%)*	*13 (16.7%)*	*29 (15.0%)*
		2	*0*	*3 (3.9%)*	*0*	*3 (1.6%)*
		3	*0*	*0*	*0*	*0*
Week 13	**Non-physiological**	**None**	**20 (52.6%)**	**10 (13.0%)**	**10 (12.8%)**	**40 (20.7%)**
		1	**9 (23.7%)**	**11 (14.3%)**	**9 (11.5%)**	**29 (15.0%)**
		2	**3 (7.9%)**	**14 (18.2%)**	**15 (19.2%)**	**32 (16.6%)**
		3	**0**	**32 (41.6%)**	**29 (37.2%)**	**61 (31.6%)**
	Epithelial changes present	*None*	*20 (52.6%)*	*10 (13.0%)*	*10 (12.8%)*	*40 (20.7%)*
		1	*10 (26.3%)*	*12 (15.6%)*	*11 (14.1%)*	*33 (17.1%)*
		2	*2 (5.3%)*	*16 (20.8%)*	*14 (17.9%)*	*32 (16.6%)*
		3	*0*	*29 (37.7%)*	*28 (35.9%)*	*57 (29.5%)*
	Extensive cyst formation	*None*	*31 (81.6%)*	*27 (35.1%)*	*24 (30.8%)*	*82 (42.5%)*
		1	*1 (2.6%)*	*16 (20.8%)*	*15 (19.2%)*	*32 (16.6%)*
		2	*0*	*7 (9.1%)*	*10 (12.8%)*	*17 (8.8%)*
		3	*0*	*17 (22.1%)*	*14 (17.9%)*	*31 (16.1%)*
	Unusual vascular changes present	*None*	*22 (57.9%)*	*18 (23.4%)*	*16 (20.5%)*	*56 (29.0%)*
		1	*8 (21.1%)*	*22 (28.6%)*	*23 (29.5%)*	*53 (27.5%)*
		2	*2 (5.3%)*	*23 (29.9%)*	*23 (29.5%)*	*48 (24.9%)*
		3	*0*	*4 (5.2%)*	*1 (1.3%)*	*5 (2.6%)*
Week 38	**Non-physiological**	**None**	**26 (68.4%)**	**45 (58.4%)**	**47 (60.3%)**	**118 (61.1%)**
		1	**4 (10.5%)**	**12 (15.6%)**	**12 (15.4%)**	**28 (14.5%)**
		2	**1 (2.6%)**	**5 (6.5%)**	**1 (1.3%)**	**7 (3.6%)**
		3	**0**	**1 (1.3%)**	**3 (3.8%)**	**4 (2.1%)**
	Epithelial changes present	*None*	*26 (68.4%)*	*46 (59.7%)*	*48 (61.5%)*	*120 (62.2%)*
		1	*4 (10.5%)*	*12 (15.6%)*	*11 (14.1%)*	*27 (14.0%)*
		2	*1 (2.6%)*	*4 (5.2%)*	*2 (2.6%)*	*7 (3.6%)*
		3	*0*	*1 (1.3%)*	*2 (2.6%)*	*3 (1.6%)*
	Extensive cyst formation	*None*	*31 (81.6%)*	*56 (72.7%)*	*59 (75.6%)*	*146 (75.6%)*
		1	*0*	*6 (7.8%)*	*2 (2.6%)*	*8 (4.1%)*
		2	*0*	*0*	*1 (1.3%)*	*1 (0.5%)*
		3	*0*	*1 (1.3%)*	*1 (1.3%)*	*2 (1.0%)*
	Unusual vascular changes present	*None*	*27 (71.1%)*	*52 (67.5%)*	*50 (64.1%)*	*129 (66.8%)*
		1	*4 (10.5%)*	*8 (10.4%)*	*13 (16.7%)*	*25 (13.0%)*
		2	*0*	*3 (3.9%)*	*0*	*3 (1.6%)*
		3	*0*	*0*	*0*	*0*

Note: Summaries only include subjects where no hysterectomy or endometrium ablation was performed prior to Visit 8 (Week 38).
Denominator of percentage is the number of subjects where no hysterectomy or endometrium ablation was performed.

Presence of Ovarian Cyst with a Diameter ≥4 cm assessed by MRI at Week 13 Visit

The presence of ovarian cysts ≥ 4 cm was determined by MRI at screening and at treatment completion (Week 13). In addition, transvaginal ultrasound of the ovaries was performed at screening

for assessment of the inclusion criterion and at Week 17 if abnormalities had been detected at the Week 13 MRI. Subjects with ovarian cysts ≥ 4 cm at the screening ultrasound were to be excluded from the study. Two subjects in the ulipristal 5 mg and 10 mg respectively had persistent cysts from screening to week 13. Most of the subjects with temporary cysts (13 cases) were treated with ulipristal. Only one case of ovarian cyst was reported at week 13 in placebo.

Ultrasound of Ovary (Normal/Abnormal) at Screening and Week 17 Visits

Ultrasound of the ovaries was systematically performed at screening, in order to assess the inclusion criterion, and at Week 17 if abnormalities were detected at Week 13 MRI. A number of cysts were observed at various stages of the study for all treatment groups. The background incidence of cysts and the persistence of some of these cysts for periods of a few weeks or more in line with other cross sectional surveys of the incidence of cysts in women of reproductive age who are not taking oral contraceptives. Two subjects in the ulipristal acetate5 mg and one in the 10 mg respectively had persistent cysts from screening to week 17. No subjects with cysts were observed in the placebo group.

Return to Menstruation after end of Treatment, Week 38

Of subjects who did not undergo hysterectomy or endometrium ablation, 98% of subjects In the placebo group had return to menstruation at week 38. The corresponding figures for ulipristal acetate 5 mg and 10 mg were 99% % and 95% % respectively. Subjects who received ulipristal acetate returned to menstruation after a mean duration of 27 to 33 days. The majority of subjects who received placebo continued to menstruate throughout the study, so mean time to first menstruation after the end of treatment was only 22 days.

Study PGL07-022

In Study PGL07-022, the primary safety objective was to demonstrate superior safety and tolerance of ulipristal acetate (PGL4001) versus GnRH-agonist regarding castration-related symptoms and their consequences of which the principal parameters are serum estradiol levels and hot flushes. A general summary of the adverse events recorded in Part A of the study, for the safety population, is described in the table below.

Table 31. General Summary of Adverse Events Part A (Safety Population)

	Treatment Group								
	PGL4001 5mg (N=97)			PGL4001 10mg (N=103)			GnRH-agonist (N=101)		
	n	N	%	n	N	%	n	N	%
At Least One Adverse Event	240	76	78.4	283	85	82.5	348	90	89.1
At Least One TEAE	216	75	77.3	254	79	76.7	323	85	84.2
At Least One Severe TEAE	11	8	8.2	5	5	4.9	26	16	15.8
At Least One Study Medication Related TEAE	103	57	58.8	102	53	51.5	150	71	70.3
At Least One Serious TEAE	5	5	5.2	4	4	3.9	4	4	4.0
At Least One Serious Study Medication Related TEAE	0	0	0.0	2	2	1.9	0	0	0.0
TEAE With Action Taken Study Drug Discontinued	1	1	1.0	4	2	1.9	13	6	5.9
TEAE Leading to Study Withdrawal	1	1	1.0	4	2	1.9	11	5	5.0

n: No of events.
N: Number of subjects with events
%: 100% x (No of subjects with event / No of subjects)

The frequency of TEAEs reported by subjects in the GnRH- agonist group appeared to be slightly higher due to the increased incidence of hot flushes and psychiatric disorders (e.g. insomnia) reported. At least one treatment emergent adverse events (TEAE) were reported by 84 % of the GnRH-agonist group compared to 77 % in the ulipristal groups. The most common TEAE was hot flush, which was reported more frequently by subjects from the GnRH-agonist group.

Table 32. Summary of Treatment Emergent Adverse Events Occurring in ≥3% of the Subjects in any Treatment Group Presented by System Organ Class and Preferred Term Part A (Safety Population) in Study PGL07-022

	Treatment Group								
	PGL4001 5mg (N=97)			PGL4001 10mg (N=103)			GnRH-agonist (N=101)		
System Organ Class / Preferred Term	**n**	**N**	**%**	**n**	**N**	**%**	**n**	**N**	**%**
At least one Treatment Emergent Adverse Event	216	75	77.3	254	79	76.7	323	85	84.2
Reproductive system and breast disorders	50	39	40.2	61	44	42.7	103	70	69.3
Hot flush	26	25	25.8	26	25	24.3	79	66	65.3
Dysmenorrhoea	6	4	4.1	5	5	4.9	2	2	2.0
Pelvic pain	4	3	3.1	5	5	4.9	3	3	3.0
Ovarian cyst	1	1	1.0	5	5	4.9	3	2	2.0
Breast pain	4	4	4.1	1	1	1.0	2	2	2.0
Nervous system disorders	47	30	30.9	33	27	26.2	62	34	33.7
Headache	38	25	25.8	24	19	18.4	49	29	28.7
Migraine	3	2	2.1	3	3	2.9	6	3	3.0
Gastrointestinal disorders	19	17	17.5	33	21	20.4	35	22	21.8
Abdominal pain	3	3	3.1	10	9	8.7	9	9	8.9
Nausea	6	6	6.2	7	7	6.8	6	6	5.9
Abdominal pain upper	3	3	3.1	3	3	2.9	7	5	5.0
Diarrhoea	2	2	2.1	2	2	1.9	5	3	3.0
Constipation	3	3	3.1	2	2	1.9	1	1	1.0
Vomiting	1	1	1.0	1	1	1.0	4	4	4.0
Infections and infestations	20	14	14.4	19	16	15.5	23	16	15.8
Nasopharyngitis	6	6	6.2	4	4	3.9	2	2	2.0
Influenza	2	2	2.1	2	2	1.9	5	5	5.0
Pharyngitis	5	5	5.2	0	0	0.0	2	2	2.0
Vaginal infection	0	0	0.0	2	2	1.9	3	3	3.0
Injury, poisoning and procedural complications	13	12	12.4	18	17	16.5	15	12	11.9
Procedural pain	10	9	9.3	15	15	14.6	12	9	8.9
Musculoskeletal and connective tissue disorders	10	8	8.2	15	13	12.6	15	10	9.9
Back pain	4	4	4.1	3	3	2.9	5	4	4.0
Arthralgia	2	2	2.1	4	4	3.9	3	3	3.0
Muscle spasms	2	2	2.1	2	2	1.9	3	3	3.0
General disorders and administration site conditions	7	7	7.2	21	17	16.5	11	9	8.9
Fatigue	4	4	4.1	8	7	6.8	3	3	3.0
Asthenia	0	0	0.0	4	4	3.9	1	1	1.0
Skin and subcutaneous tissue disorders	5	5	5.2	12	11	10.7	14	13	12.9
Acne	0	0	0.0	6	5	4.9	5	5	5.0
Hyperhidrosis	1	1	1.0	0	0	0.0	3	3	3.0
Psychiatric disorders	5	4	4.1	6	4	3.9	15	13	12.9
Insomnia	2	2	2.1	2	2	1.9	5	5	5.0
Blood and lymphatic system disorders	6	6	6.2	3	3	2.9	5	5	5.0

n: No of events.
N: Number of subjects with events
%: 100% x (No of subjects with event / No of subjects)

Headache was the second most frequently reported TEAE, experienced by 25.8% of subjects from the PGL4001 5 mg group, 18.4% of subjects from the PGL4001 10 mg group and 28.7% of subjects from the GnRH-agonist group.

The majority of TEAEs were assessed as mild or moderate for all treatment groups. Severe TEAEs were reported in 15% in the GnRH – agonist compared to 5-8% in the ulipristal acetate groups. Eight subjects withdrew from the study due to TEAEs; for 5 of these the AEs were considered related to study drug and these included: insomnia, hand tremor and anxiety (PGL4001 10 mg), worsening of uterine bleeding (PGL4001 10 mg), migraine (GnRH-agonist), headaches, pruritus and breast pain (GnRH-agonist) and hot flushes, sweating and insomnia (GnRH-agonist). Three subjects withdrew from the study due to the unrelated SAEs of sarcoma (PGL4001 5 mg group), lymphocytic cerebrospinal meningitis (GnRH-agonist) and worsening of uterine bleeding (GnRH-agonist). a majority of TEAEs > 3% were related to the reproductive system and the breast.

Mean serum estradiol (E2) levels at end of treatment visit (Week 13 visit) for PGL4001 compared with GnRH-agonist

The mean E2 levels were significantly higher in the ulipristal acetate groups compared to GnRH-agonist treated women at week 13.

Percentage of subjects reporting moderate or severe hot flushes as adverse events throughout the treatment period for PGL4001 compared with GnRHagonist.

More than 60% of the GnRH-agonist treated women complained of hot flushes compared to about one fourth of the ulipristal acetate treated women ($p < 0.001$).

Analysis of other Castration-related symptoms

Women in all three treatment groups experienced other castration-related symptoms. Most of them were mild. Moderate symptoms were only reported in the GnRH-agonist group.

Bone turnover assessed by blood and urinary dosage of biochemical markers of bone-resorption and bone-formation at Week 9 and Week 13 visits

The limited duration of treatment showed no impact on bone turnover in women treated with ulipristal acetate. For GnRH-agonist a significant effect was observed only in one out of four markers (CTX) used at week 13.

Endometrium thickness assessed by ultrasound at Week 13 and Week 17 visits

The distribution of endometrial thickness was similar at screening for the three treatment groups. Around 5% of the women had a thickness > 16 mm. At the end of treatment the corresponding figures for ulipristal acetate 5 mg and 10 mg respectively was 11.3% and 14.6 %, with only one case > 16 mm reported in the GnRH-agonist group ($p < 0.001$). Among women who did not undergo hysterectomy or endometrial ablation, there were no significant difference in endometrium thickness at screening or at week 17 visit between the treatments assessed by ultrasound.

Ultrasound of ovary (normal/abnormal) at Week 13 visit, and Week 17 visits if abnormal ovaries were detected at ultrasound at Week 13 visit and no ovariectomy was performed

Ultrasound of ovaries showed that one subject in the ulipristal acetate 5 mg, 10 mg and GnRH-agonist group respectively had persistent cysts from screening to week 17. At week 13 all subjects with temporary cysts were treated with ulipristal acetate.

Endometrium biopsy (diagnosis) using pre-defined histological classification

Evaluation of endometrial biopsies showed that 90-97 % of the biopsies were adequate at screening. Three benign lesions were diagnosed in the ulipristal acetate 5 mg group and one in the GnRH-agonist group. At week 13, 87-92 % of the biopsies were adequate, and two cases of benign lesions were diagnosed in the ulipristal acetate 5mg group and one from each of the 10 mg and GnRH-agonist groups. It was a different subject in the ulipristal 5 mg group who had a simple, non-atypical hyperplasia at week 13 than at screening.

At screening, the proportion without non-physiological endometrium biopsies was about 80 % in all treatment groups. When the endometrium biopsies were reviewed by the three independent expert pathologists, there was a consensus diagnosis of only one non-physiological endometrium in the ulipristal acetate 10 mg group at screening. At week 13 the subjects treated with ulipristal acetate (PGL4001) had findings without non-physiological endometrium in 20-23 % compared to 64% in the GnRH group. Epithelial changes were present in 35.0 – 37.1 % in the ulipristal groups vs 1 % in the GnRH-agonist group. There was also a very wide variation between the pathologists in the histopathologic evaluation.

In the subset of patients who did not undergo surgery after the end of treatment, results of the evaluation of endometrium biopsies at week 38 suggest that while ulipristal acetate treatments increased findings of non-physiological changes at week 13, maintenance of this effect stopped after treatment discontinuation. The proportion with information on biopsies was 81% in the GnRH-agonist group and 82 and 84% in ulipristal acetate 5 mg and 10 mg groups respectively.

In addition, at week 38, the number of biopsies with non-physiological changes present was low in all treatment groups. The absolute number of non-physiological changes (8) was however greatest in the ulipristal acetate 5 mg group, and higher than the numbers at screening (4).

Return to Menstruation after end of Treatment, Week 38

In the GnRH-agonist group 96.2% had return to menstruation at week 38. The corresponding figures for ulipristal acetate 5 mg and 10 mg were 100 % and 97 % respectively. Subjects who received ulipristal acetate returned to menstruation after a mean duration of 31 to 34 days. The return to menstruation following treatment with leuprorelin was longer than that seen with ulipristal acetate (43 days).

Serious adverse event / deaths / other significant events

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

Study PGL07-021

Table 33. Summary of Serious Adverse Events from screening to week 17 Study PGL07-021 (Safety Population)

No. of days on treatment	Subject ID	Severity	Causality Reporter:	Therapy start Therapy stop Date of onset	Main event (PT) *Verbatim* Other symptoms	Outcome
Placebo						
Treatment period 26 days	142/1026	Severe	Not related	26-FEB-2009 01-JUN-2009 24-MAR-2009	**Uterine leiomyoma** *Nascent submucous leiomyoma of uterus*	Resolved
Follow-up period 1 month after last dose	115/1118	Severe	Not related	31-MAR-2009 15-JUN-2009 21-JUL-2009	**Breast cancer** *Breast cancer*	Not resolved
PGL4001 5 mg						
Follow-up period 14 days after last dose	146/1190	Moderate	Not related	20-MAY-2009 27-AUG-2009 10-SEP-2009	**Uterine hemorrhage** *Uterine bleeding*	Resolved
Follow-up period 21 days after last dose	144/1044	Mild	Not related	02-FEB-2009 28-APR-2009 19-MAY-2009	**Ovarian hemorrhage** *Ovarian hemorrhage secondary to rupture of cyst*	Resolved
PGL4001 10 mg						
Treatment period 79 days	100/1017	Severe	Not related	08-DEC-2008 01-MAR-2009 25-FEB-2009	**Uterine hemorrhage** *Strong uterine bleeding*	Resolved

Table 34. Serious Adverse Events during the Screening Period

Screening period	150/1157	Severe	Not related	Unknown Unknown 13-MAR-2009	**Appendicitis** *Acute Gangrenous Appendicitis Uterine leiomyoma Peritonitis*	Resolved with sequelae
Screening period	141/1217	Moderate	Not related	Unknown Unknown 28-APR-2009	**Uterine hemorrhage** *Worsening of uterine bleeding*	Resolved
Screening period	148/1284	Moderate	Not related	Unknown Unknown 21-JUN-2009	**Uterine hemorrhage** *Worsening of uterine bleeding*	Resolved

The eight serious Adverse Events in study PGL07-021 were considered not related to the treatment.

PGL07-022

Table 35. Summary of Serious Adverse Events to week 17 Study PGL07-022 (Safety Population)

N° of days on treatment until SAE reported	Patient ID	Severity	Causality Investigator:	Therapy start Therapy stop Date of onset	Main event (Preferred Term) *Verbatim* Other symptoms	Outcome
PGL4001 5 mg						
Treatment period 21 days	281/5370	Moderate	Not related	13-JUL-2009 11-OCT-2009 03-AUG-2009	**Headache** *Headache*	Resolved
Treatment period 74 days	283/5189	Severe	Not related	07-MAY-2009 06-AUG-2009 20-JUL-2009	**Thyroid cancer** *Carcinoma planuepitheliale glanduli thryroidei*	Resolved
Follow up period 2 days after last dose (Pelvic pain from 17-JUL-2009)	210/5329	Severe	Not related	16-JUN-2009 03-AUG-2009 05-AUG-2009	**Sarcoma** *Sarcoma*	Not resolved
Follow-up period 2 days after last dose	251/5202	Moderate	Not related	05-MAY-2009 27-JUL-2009 29-JUL-2009	**Post procedural complication** *Suspected perforation of the uterus during hysteroscopy*	Resolved
Follow-up period 10 days after last dose	251/5296	Moderate	Not related	25-MAY-2009 22-AUG-2009 01-SEP-2009	**Operative hemorrhage** *Blood loss during laparoscopic assisted myomectomy*	Resolved
PGL4001 10 mg						
Treatment period 29 days	283/5239	Severe	Related	26-MAY-2009 24-AUG-2009 24-JUN-2009	**Leiomyoma** *Protruded myoma nascens**	Resolved
Follow up period 2 days after last dose. (Non-serious AE uterine bleeding from 15-May-2009)	282/5196	Severe	Related	29-APR-2009 21-MAY-2009 23-MAY-2009	**Uterine hemorrhage** *Worsening of uterine bleeding*	Resolved
Follow-up period 19 days after last dose	276/5160	Mild	Not related	03-APR-2009 28-JUN-2009 17-JUL-2009	**Uterine polyp** *Endometrial polyp*	Resolved
Follow-up period 1 month after last dose	272/5011	Moderate	Not related	26-NOV-2008 25-FEB-2009 24-MAR-2009	**Hemangioma** *Vertebral angioma*	Not resolved

GnRH-agonist						
Treatment period 28 days (28 days after last leuprorelin injection)	254/5100	Severe	Not related	17-MAR-2009 13-APR-2009 14-APR-2009	**Uterine hemorrhage** *Worsening of bleeding*	Resolved
Treatment period 80 days (18 days after last leuprorelin injection)	277/5284	Severe	Not related	14-MAY-2009 19-AUG-2009 02-AUG-2009	**Lung infection** *Pulmonary infection*	Resolved
Follow up period 8 days after last leuprorelin injection (3-Jun-2009) (1 day after last dose of placebo) (Headache since APR-2009)	284/5175	Severe	Not related	06-APR-2009 10-JUN-2009 11-JUN-2009	**Choriomeningitis lymphocytic** *Lymphocytic cerebrospinal meningitis*	Resolved
Follow-up period 44 days after last leuprorelin injection (10 day after last dose of placebo)	271/5030	Severe	Not related	27-JAN-2009 26-APR-2009 07-MAY-2009	**Wound hemorrhage** *Post-operative wound bleeding*	Resolved

Of 13 serious adverse events in study PGL07-022 were two cases considered related to the treatment with ulipristal acetate.

Laboratory findings

Study PGL07-021

Summary of hormone tests at baseline, week 13 and week 17

• Estradiol (E2)

Subjects under ulipristal acetate treatment were mainly anovulatory. E2 values observed under PGL4001 treatment correspond to mid-follicular phase levels for pre-menopausal women. The increase in estradiol levels after treatment cessation demonstrates that ovarian function and follicular development resume promptly within a few weeks after treatment end.

• Progesterone (P4)

Progesterone levels are reported in the table below as a parameter indicating whether a subject ovulated within approximately 2 weeks preceeding the sampling time. A progesterone level above 5 ng/mL is usually considered as evidence of ovulation.

Table 36: Progesterone values from baseline to week 17 Study PGL07-021

Visit	Parameter	Value	Placebo	Ulipristal acetate 5 mg	Ulipristal acetate 10 mg
Baseline	P4	N	46	88	96
		Mean	0.48	0.71	0.79
		SD	0.64	1.33	1.41
		Median	0.30	0.30	0.40

		Min, Max	0.1, 3.8	0.1, 9.1	0.1, 11.5
Week 13		N	47	89	90
		Mean	3.08	0.58	0.42
		SD	4.59	1.28	1.35
		Median	0.70	0.30	0.25
		Min, Max	0.1, 19.7	0.1, 7.6	0.1, 13.0
Week 17		N	44	88	88
		Mean	2.83	2.94	2.75
		SD	3.91	4.55	4.53
		Median	0.65	0.50	0.50
		Min, Max	0.1, 14.4	0.1, 27.8	0.1, 22.6

The mean progesteron values in the ulipristal acetate group were lower than in the placebo at week 13 indicating anovulation in a majority of patients. However, maximal values above 5.0 ng/mL indicate persistence of ovulation in a minority of women treated with ulipristal acetate compared to placebo.

• Adrenocorticotropic Hormone (ACTH)

ACTH values were monitored as a marker of anti-glucocorticoid effect of ulipristal acetate. Median ACTH values showed little change throughout the treatment period for all treatment groups. Based on the confidence intervals, there was no evidence of a difference in the ACTH levels between the ulipristal acetate treatment groups and the placebo group.

• Thyroid-Stimulating Hormone (TSH)

There was no evidence of a difference in TSH profile for the ulipristal acetate treatment groups compared to the placebo group during the treatment period. There was no evidence of a difference in TSH profile for the ulipristal acetate treatment groups compared to the placebo group during the treatment period. In addition, a review of AEs in relation to thyroid function did not reveal a treatment related effect.

• Prolactin

During the treatment period the prolactin values across the three groups showed some variation with no obvious finding related to the ulipristal acetate treatment.

• FSH

The median values for FSH at baseline were 9.25, 8.50 and 8.70 mIU/mL for the placebo, ulipristal acetate 5 mg and 10 mg groups, respectively. The values were lower at Week 13, being 7.40 mIU/mL, 5.70 mIU/mL and 5.00 mIU/mL, respectively. There was some evidence of a difference in FSH between the ulipristal acetate treatment groups and placebo at Week 13. There was no impact of ulipristal acetate treatment on glucose.

There were increases in mean triglycerides, cholesterol, and LDL cholesterol from baseline to end of treatment for all three treatment groups. The increases from baseline in mean cholesterol and LDL cholesterol levels were greater for the ulipristal acetate treatment groups than for the placebo group. The baseline values were higher for the placebo group compared to the ulipristal acetate treated groups.

Mildly elevated transaminase levels, most frequently ALT and AST, were reported for approximately 5% of subjects in all 3 treatment groups; the distribution of subjects with high values was similar across the three treatment groups. In general the elevations were less than 2 x ULN, transient and not combined with any change in other biochemical parameters including bilirubin levels.

Study PGL-0722

Summary of hormone tests at baseline, Week 5, Week 9, Week 13 and Week 17

- Progesterone

During treatment, the mean and median P4 values were very low in all treatment groups suggesting the absence of ovulation in most subjects. Maximal values close to or above 5.0 ng/mL in all groups indicate persistence of ovulation in a minority of subjects (< 10%).

- ACTH

All three treatment groups had similar values for ACTH though the mean values were slightly higher for subjects from the GnRH-agonist group at Weeks 5, 9 and 13. There is no evidence of a difference for GnRH-agonist treatment compared to the ulipristal acetate treatments based on the p-values and confidence intervals.

- TSH

TSH values at baseline were higher in the ulipristal acetate 10 mg group (7 subjects, 6.8%) compared to the GnRH-agonist group (3 subjects, 3.0%). There is no evidence for a difference at Week 13 or Week 17, or for ulipristal acetate 5 mg compared to GnRH-agonist values.

- Prolactin

The mean and median prolactin values remained unchanged during treatment in the ulipristal acetate groups. At Week 5 the mean prolactin levels were lower for subjects from the GnRH-agonist group compared to subjects from the ulipristal acetate 5 mg and 10 mg groups ($p < 0.001$).

There was a difference between ulipristal acetate 5 mg and GnRH-agonist values at Week 9 (p-value=0.013). There is no evidence of a difference at Week 13 or Week 17. The reduction observed in the GnRH-agonist group most likely is the consequence of the reduction of E2 in this group.

- FSH

The median values for FSH at baseline were 7.95 mIU/mL, 8.80 mIU/mL and 9.20 mIU/mL for the ulipristal acetate 5 mg, 10 mg and GnRH-agonist groups respectively. The values were lower at Week 13: 4.80 mIU/mL, 4.90 mIU/mL and 5.80 mIU/mL respectively. There is evidence of a difference in

FSH between the ulipristal acetatetreatments and GnRH-agonist at Week 13 (p-value=0.021 for ulipristal acetate 5 mg and p-value=0.031 for PGL4001 10 mg).

- Serum estradiol (E2) levels at baseline, Week 5, Week 9 and Week 17 visits.

At Week 13 the median E2 values were 64.0 pg/mL, 60.5 pg/mL and 25.0 pg/mL for women from the ulipristal acetate 5 mg and 10 mg group and GnRH-agonist group, respectively. The summaries of the E2 levels at Weeks 5 and 9 also showed comparable differences between ulipristal acetate groups and GnRH-agonist. Within a few weeks after all treatment discontinuation, the increase in E2 levels demonstrated that ovarian function, and follicular development had resumed.

- Hematology, coagulation, biochemistry, lipids, and glucose assessments at screening, baseline, Week 5, Week 9, Week 13, Week 17 visits

There was no impact on glucose levels during treatment. Ulipristal treatment was associated with a slight rise in mean total cholesterol and mean LDL cholesterol during treatment, but these increases were lower than those observed in women treated with GnRH-agonist.

Overall the percentage of subjects with Hb > 12 g/dL and Hct > 36% increased during the study. Parameters of coagulation did not identify any trends towards modification, with only 3 clinically significant values reported, 2 for prothrombin time and one for APTT, which were slightly greater than the ULN.

There were no signals of any treatment related changes in liver function tests.

Safety in special populations

No safety studies in special populations were submitted.

Safety related to drug-drug interactions and other interactions

See Pharmacokinetic section.

Discontinuation due to adverse events

No subject withdrew from the Study PGL07-021 due to TEAEs. In Study PGL07-022 eight subjects withdrew from the study due to TEAEs; for 5 of these the AEs were considered related to study drug and these included: insomnia, hand tremor and anxiety (PGL4001 10 mg), worsening of uterine bleeding (PGL4001 10 mg), migraine (GnRH-agonist), headaches, pruritus and breast pain (GnRH-agonist) and hot flushes, sweating and insomnia (GnRH-agonist). Three subjects withdrew from the study due to the unrelated SAEs of sarcoma (PGL4001 5 mg group), lymphocytic cerebrospinal meningitis (GnRH-agonist) and worsening of uterine bleeding (GnRH-agonist).

Post marketing experience

No post-marketing studies have been submitted.

2.6.1. Discussion on clinical safety

In the present submission, the majority of the clinical safety data have been drawn from 4 randomized, double-blind, repeated-dose studies carried out in the target population. In addition to the safety database included in the initial submission, the applicant has provided additional safety data.

Complete 6-month, post-treatment clinical study reports of the pivotal phase III studies (PGL07-021 and PGL07-022 Part B CSRs) and interim safety analysis from the ongoing Phase IIIb Study PGL09-026 provides data on a further 124 subjects of which 110 received ulipristal acetate 10 mg daily for at least 12 weeks. The inclusion of the subjects from study PGL09-026 increases the number of patients having been exposed to at least 3 months of ulipristal acetate to the target dose of 5 mg or above to a total of 529 subjects.

Safety assessments included reporting of adverse events in all studies. Other safety assessments varied, but included physical examinations, vital signs, 12-lead electrocardiogram (ECG) recording, biological laboratory assessments, ovarian scans, measurement of endometrium thickness, and endometrial biopsies.

In the pivotal studies the safety endpoint was to assess overall safety of ulipristal acetate (PGL4001) in subjects with uterine myomas, and to demonstrate superior safety and tolerance of PGL4001 versus GnRH-agonist regarding castration-related symptoms and their consequences.

In Study PGL07-021, the proportion of subjects reporting at least one study medication related treatment emergent adverse events (TEAEs) was in the ulipristal acetate groups 22.4-18.9% compared to 8.3% placebo. Corresponding values in PGL07-022 were reported by 84 % of the GnRH-agonist group compared to 77 % in the ulipristal acetate groups. Hot flush was reported more frequently by subjects from the GnRH-agonist group.

Amongst the adverse reactions documented with ulipristal acetate treatment, hot flush, headache, ovarian cysts, uterine haemorrhage and endometrial thickening were noteworthy. Hot flush was reported more frequently by subjects treated with the GnRH-agonist compared to ulipristal acetate treated. Therefore section 4.8 of the SmPC states that hot flushes were reported by 12.7% patients but the rates varied across trials. In the active comparator controlled study the rates were 24% (10.5% moderate or severe) for ulipristal acetate and 60.4% (39.6% moderate or severe) for leuprorelin-treated patients. In the placebo-controlled study, the rate of hot flushes was 1.0% for ulipristal acetate and 0% for placebo.

Mild or moderate severity headache was reported in 6.4% of patients. Functional ovarian cysts were observed during and after treatment in 1.5% of patients and in most of the cases spontaneously disappeared within a few weeks. Patients with heavy menstrual bleeding due to uterine fybroids are at risk of excessive bleeding, which may require surgical intervention. A few cases have been reported during Esmya treatment or within 2-3 months after ulipristal acetate treatment was stopped.

Assessments of the ovaries during the studies were performed with transvaginal ultrasound or MRI. Most of the subjects with temporary cysts were treated with ulipristal acetate. The background incidence of cysts and the persistence of some of these cysts for periods of a few weeks or more were in line with other cross sectional surveys of the incidence of cysts in women of reproductive age who are not taking oral contraceptives.

The median time for menstruation return was for the ulipristal acetate treated group about one week later than with the placebo, and within one month after end of treatment. In GnRH-agonist treated women, the median time for menstruation return was about 43 days.

Bone turnover was assessed by blood and urinary dosage of four biochemical markers of bone-resorption and bone-formation at Week 9 and Week 13 visits. For GnRH-agonist a significant increase was observed only in one out four markers (CTX, a marker of bone resorption) used at week 13, whereas no effect was recorded with ulipristal acetate.

Subjects under ulipristal acetate treatment were mainly anovulatory. During the treatment period, the laboratory values across the treatment groups showed some variation with no obvious finding related to the ulipristal acetate treatment.

Assessments with magnetic resonance imaging (MRI) or ultra-sound (US) showed at week 13 more subjects in the ulipristal acetate treated groups with endometrium thickness > 16 mm compared to placebo or GnRH-agonist treated groups. The increase appears to be reversible. Therefore, information in the SmPC includes the occurrence of increased thickening of the endometrium, a documented incidence of up to 15% of patients who may experience a thickening exceeding 16mm, and the need to investigate such thickening if persisting more than 3 months following the end of treatment and return

of menstruation. Additionally, an educational program has been agreed to enforce this information (see Section 2.7 Pharmacovigilance)

Treatment of progesterone receptor modulators (PRMs) results in new endometrial findings, described under the name of Progesterone Receptor Modulator Associated Endometrial Changes (PAEC). The rating scale used to evaluate the endometrium biopsies in the pivotal Phase III trials incorporated the description of these non-physiological findings that are the result of PRM treatment, and followed generally accepted recommendations for endometrial biopsy assessment. The rating scale to assess the endometrial biopsies is therefore considered adequate.

At Week 13 (PGL07-021), the numbers of subjects with endometrium biopsies for which all three pathologists reported “non-physiological” changes in the endometrium (PAEC) was no case (0.0%) in the placebo group, and 43 (45.3%) cases and 37 (37.8%) cases in the PGL4001 5 mg and 10 mg groups, respectively. Corresponding figures for PGL07-022 was in the GnRH-agonist group 2 (2.0%), vs. 38 (39.2%) and 40 (38.8%) for ulipristal acetate 5 mg and 10 mg groups respectively. The transformation was associated with a significant reduction in proliferative endometrium.

Observed non-clinical endometrial changes in the 9-month monkey toxicity study with a 2-month recovery period in selected control and high dose animals (25 mg/kg/day), ulipristal acetate-related microscopic changes occurred in a dose dependent pattern in the uterus and oviducts. Two clinical pathologists were evaluating the biopsies. It was concluded that since the observed effects are less frequent in the recovery animals of the high dose group, the effects are at least partly reversible.

Dose-related pharmacologically mediated effects were noted which to a considerable extent resemble those observed in human endometrium exposed to PRMs referred to as PAEC, rather than an unopposed oestrogen effect, as the glandular epithelium was less active with little evidence of proliferative activity.

Endometrial data at week 38 in Study PGL07-021 and Study PGL07-022 is reassuring regarding diagnosis of malignant changes, cellular atypia or other findings of concern in the ulipristal acetate treatment groups. The incidence of PAEC at week 38 (6 months after end of treatment) was similar to that observed at screening. Diverging results of the histopathologic endometrial assessments between pathologists underlines the need of PAEC trained pathologists to avoid misdiagnosis in clinical routine.

The short-term safety data after 3 months of treatment with ulipristal acetate do not show an increased risk for malignant changes in the endometrium (studies PGL07-021, PGL07-022. and interim safety analysis of PGL09-026)). The long-term endometrial safety data of PAEC will also be followed in the ongoing phase III clinical study (PGL09-026), its extension (PGL09-027), a non-interventional study (PGL10-014) and a retrospective drug utilization study (PGL11-020). Considering the indication is limited to treatment duration of a maximum 3 months including a contraindication for treatment beyond this duration, no major safety issues remain.

Based on the clinical safety data submitted, the Product Information has been amended as follows:

Section 4.2 of the SmPC notes that here are no data available on treatment with duration longer than 3 months or on repeat courses of treatment, therefore, treatment duration should not exceed 3 months.

Section 4.4. of SmPC notes that ulipristal acetate has a specific pharmacodynamic action on the endometrium. Increase in thickness of the endometrium may occur. If the endometrial thickening persists within the 3 months following the end of treatment and return of menstruations, this may need to be investigated as per usual clinical practice to exclude underlying conditions.

Changes in the histology of the endometrium may be observed in patients treated with ulipristal acetate. These changes are reversible after treatment cessation. These histological changes are denoted as "Progesterone Receptor Modulator Associated Endometrial Changes" or PAEC and should not be mistaken for endometrial hyperplasia

Section 4.8 of the SmPC notes that in 10-15% of patients, thickening of the endometrium (> 16 mm by ultrasound or MRI at end of treatment) was observed with ulipristal acetate; this reverses when treatment is stopped and menstrual periods resume.

In addition, reversible changes to the endometrium are denoted PAEC and are different from endometrium hyperplasia. If hysterectomy or endometrial biopsy specimens are sent for histology, then the pathologist should be informed that the patient has been prescribed ulipristal acetate .

Section 5.1 of the SmPC notes that in about 10-15% of patients treated with ulipristal acetate the endometrium may thicken (>16 mm) during treatment. This thickening disappears after treatment is withdrawn and menstruation occurs. If the endometrial thickness persists within the 3 months following the end of treatment and return of menstruations, then this may need to be investigated as per usual clinical practice to exclude underlying conditions.

The direct action on the endometrium results in class-specific changes in histology termed PAEC. Typically, the histological appearance is an inactive and weakly proliferative epithelium associated with asymmetry of stromal and epithelial growth resulting in prominent cystically dilated glands with admixed oestrogen (mitotic) and progestin (secretory) epithelial effects. Such a pattern has been observed in approximately 60% of patients treated with ulipristal acetate for 3 months. These changes are reversible after treatment cessation. These changes should not be confused with endometrial hyperplasia.

2.6.2. Conclusions on the clinical safety

The safety profile of Esmya is considered acceptable and all the adverse reactions reported in clinical trials have been included in the Product Information.

An ongoing phase III study (PGL09-026), and its extension, (PGL09-027) will address the long term effect of prolonged treatment of the endometrium with ulipristal acetate, the risk of inappropriate management of endometrium thickening (unnecessary interventions or treatments), the risk of inappropriate diagnosis of endometrial hyperplasia (mistaking PAEC for hyperplasia).

In addition to this, the applicant will carry out a non-interventional study (PGL10-014) and a retrospective drug utilization study (PGL11-020) to further identify the impact of treatment on surgery, delays in the diagnosis of atypical endometrial hyperplasia or adenocarcinoma, and to gather more information on the risk of off label use (treatment beyond 3 months).

These post-authorisation measures have been adequately covered in the RMP.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The applicant submitted a risk management plan, which included a risk minimisation plan.

Table 37. Summary of the risk management plan

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine and additional)
Important identified risks		
Inappropriate management of endometrium thickening (unnecessary interventions or treatments).	Routine pharmacovigilance practices. Review in PSURs as event of special interest. Non-interventional study (PGL10-014). Monitoring in clinical research (AESI). PGL09-026 and PGL09-027 studies. Prescription pattern/drug utilization study (PGL11-020). Targeted follow-up of respective ADR reports.	*Risk included in the SmPC, section 4.4, 4.8 and 5.1 (including recommendation for management).* *Warning in section 4.4. of SmPC:* "Ulipristal acetate has a specific pharmacodynamic action on the endometrium. Increase in thickness of the endometrium may occur. If the endometrial thickening persists within the 3 months following the end of treatment and return of menstruations, this may need to be investigated as per usual clinical practice to exclude underlying conditions" *Pharmacodynamic properties in section 5.1. of SmPC:* "Ulipristal acetate exerts a direct effect on the endometrium...." ...In about 10-15% of patients treated with ulipristal acetate the endometrium may thicken (>16 mm) during treatment. This thickening disappears after treatment is withdrawn and menstruation occurs. If the endometrial thickness persists within the 3 months following the end of treatment and return of menstruations, then this may need to be investigated as per usual clinical practice to exclude underlying conditions." *Description of selected adverse reactions in section 4.8. of SmPC:* *"Endometrial thickening* In 10-15% of patients, thickening of the endometrium (> 16 mm by ultrasound or MRI at end of treatment) was observed with ulipristal acetate; this reverses when treatment is stopped and menstrual periods resume." Educational material to prescribers.
Inappropriate diagnosis of endometrial hyperplasia (mistaking PAEC for hyperplasia)	Routine pharmacovigilance practices. Review in PSURs as event of special interest. Non-interventional study (PGL10-014). Monitoring in clinical research (AESI). PGL09-026 and PGL09-027	*Risk included in the SmPC, section 4.4, 4.8 and 5.1.* *Warning in section 4.4. of SmPC:* "Ulipristal acetate has a specific pharmacodynamic action on the endometrium.... Changes in the histology of the endometrium may be observed in patients treated with ulipristal acetate. These changes are reversible after treatment cessation. These histological changes are denoted as "Progesterone Receptor Modulator Associated Endometrial Changes" or PAEC and should not be mistaken for endometrial hyperplasia (see sections 4.8. and 5.1.)."

	studies. Prescription pattern/drug utilization study (PGL11-020). Targeted follow-up of respective ADR reports.	*Pharmacodynamic properties in section 5.1. of SmPC:* "Ulipristal acetate exerts a direct effect on the endometrium.... The direct action on the endometrium results in class-specific changes in histology termed PAEC. Typically, the histological appearance is an inactive and weakly proliferative epithelium associated with asymmetry of stromal and epithelial growth resulting in prominent cystically dilated glands with admixed oestrogen (mitotic) and progestin (secretory) epithelial effects. Such a pattern has been observed in approximately 60% of patients treated with ulipristal acetate for 3 months. These changes are reversible after treatment cessation. These changes should not be confused with endometrial hyperplasia." *Description of selected adverse reactions in section 4.8. of SmPC:* "In addition, reversible changes to the endometrium are denoted PAEC and are different from endometrium hyperplasia. If hysterectomy or endometrial biopsy specimens are sent for histology, then the pathologist should be informed that the patient has been prescribed ulipristal acetate (see section 4.4 and 5.1)." Educational material to prescribers and pathologists.
Important potential risks		
Acute uterine bleeding requiring immediate intervention	Routine pharmacovigilance practices. Review in PSURs as event of special interest. Monitoring in clinical research (AESI). PGL09-026 and PGL09-027 studies Non-interventional study (PGL10-014).	*Risk included in the SmPC Section 4.4. :* *"Bleeding pattern* Patients should be informed that treatment with ulipristal acetate usually leads to a significant reduction in menstrual blood loss or amenorrhea within the first 10 days of treatment. Should the excessive bleeding persist, patients should notify their physician. Menstrual periods will generally return within 4 weeks after the end of the treatment course." *Risk included in the SmPC, section 4.8.* *Description of selected adverse reactions in section 4.8. of SmPC:* *Uterine haemorrhage* "Patients with heavy menstrual bleeding due to uterine fibroids are at risk of excessive bleeding, which may require surgical intervention. A few cases have been reported during ulipristal acetate treatment or within 2-3 months after ulipristal acetate treatment was stopped."
Drug induced liver injury	Routine pharmacovigilance practices. Review in PSURs as event of special interest. Monitoring in clinical research (AESI). PGL09-026 and PGL09-027 studies Non-interventional study (PGL10-014)	
Important missing information		
Treatment beyond three months	Routine pharmacovigilance practices, Review in PSURs,	*Statement in the SmPC, section 4.1., 4.2, 4.3. and 4.4..* *Indication (section 4.1 of SmPC)* "Ulipristal acetate is indicated for pre-operative

	Non-interventional study (PGL10-014) PGL09-026 and PGL09-027 studies Prescription pattern/drug utilisation study (PGL11-020)	treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age. The duration of treatment is limited to 3 months (see section 4.4) *Contra-indication (section 4.3 of SmPC)* "Due to the lack of long term safety data, the duration of treatment should not be longer than 3 months (see section 4.2. and 4.4.)" *Posology and route of administration in section 4.2. of SmPC:* "The treatment consists of one tablet of 5 mg to be taken orally once daily for up to 3 months. There are no data available on treatment with duration longer than 3 months or on repeat courses of treatment, therefore, treatment duration should not exceed 3 months."*Special Warnings and precautions for use in section 4.4 of SmPC:* "In absence of safety data for a period longer than 3 months or on repeat courses of treatment, the risk of adverse impact on the endometrium is unknown if treatment is continued; therefore, treatment duration should not exceed 3 months." Educational material to prescribers.
Long-term effects of prolonged treatment on the endometrium (including possible malignant changes)	Routine pharmacovigilance practices, Review in PSURs PGL09-026 and PGL09-027 studies	*Statement in SmPC section 4.2. Posology and route of administration:* "There are no data available on treatment with duration longer than 3 months or on repeat courses of treatment, therefore, treatment duration should not exceed 3 months."
Delayed diagnosis of atypical endometrial hyperplasia or adenocarcinoma	Routine pharmacovigilance practices, Review in PSURs Non-interventional study (PGL10-014)	*Statement in the SmPC section 4.4 (special warnings and precautions):* "Ulipristal acetate has a specific pharmacodynamic action on the endometrium. Increase in thickness of the endometrium may occur. If the endometrial thickening persists within 3 months following the end of treatment and return of menstruations, this may be investigated as per usual clinical practice to exclude underlying conditions." *Statement in the SmPC section 5.1. (pharmacodynamic properties):* "Endometrium If endometrial thickness persists within the 3 months following the end of treatment and return of menstruations, then this may need to be investigated as per usual clinical practice to exclude underlying conditions." Educational material to prescribers and pathologists.
Impact on surgery	Routine pharmacovigilance practices, Review in PSURs, Non-interventional study (PGL10-014) Prescription pattern/drug utilization study (PGL11-020).	No routine risk minimisation deemed necessary.
Use in patients with moderate to severe hepatic impairment	Routine pharmacovigilance practices, Review in PSURs, Phase I study in women with mild, moderate and severe hepatic impairment (PGL-W-001) post-approval)	*Statement in the SmPC, section 4.2, 4.4, and 5.2. Posology and method of administration in section 4.2. of SmPC:* "Hepatic impairment No dose adjustment is recommended for patients with mild hepatic impairment. In the absence of specific studies, ulipristal acetate is not recommended in patients with moderate or severe hepatic impairment, unless the patient is closely monitored (see section 4.4)."

		Special warnings and precautions for use in section 4.4. of SmPC: "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 (see section 5.2.). 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 impairement, unless the patient is closely monitored (see section 4.2)." *Pharmacokinetic properties in section 5.2. of SmPC:* "Special Populations No pharmacokinetic studies with ulipristal acetate have been performed in women with impaired renal or hepatic function."
Use in patients with severe renal impairment	Routine pharmacovigilance practices, Review in PSURs,	*Statement in the SmPC, section 4.2, 4.4. and 5.2. Posology and method of administration in section 4.2. of SmPC:* "Renal impairment No dose adjustment is recommended in patients with mild or moderate renal impairment. In the absence of specific studies, ulipristal acetate is not recommended in patients with severe renal impairment (see section 4.4. and 5.2.)." *Special warnings and precautions for use in section 4.4. of SmPC:* "Renal impairment Renal impairment is not expected to significantly alter the elimination of ulipristal acetate. In the absence of specific studies ulipristal acetate is not recommended for patients with severe renal impairment, unless the patient is closely monitored (see section 4.2)." *Pharmacokinetic properties 5.2. of SmPC*: "No pharmacokinetic studies with ulipristal acetate have been performed in women with impaired renal or hepatic function."
Co-administration with P-gp substrates	Routine pharmacovigilance practices, Review in PSURs, Phase I DDI study (post-approval).	*Statement in the SmPC, section 4.4, 4.5. and 5.2. Special warnings and precautions for use in section 4.4. of SmPC.* "Concomitant treatments Ulipristal acetate is not recommended for patients receiving P-glycoprotein (P-gp) substrates (e.g. dabigatran etexilate, digoxin) (see section 4.5)." *Interactions in section 4.5. of SmPC:* *"P-gp substrates* *In vitro* data indicate that ulipristal acetate may be an inhibitor of P-gp at clinically relevant concentrations in the gastrointestinal wall during absorption. Thus, co-administration of ulipristal acetate may increase the plasma levels of concomitant medicinal products that are substrates of P-gp. In the absence of clinical data, co-administration of ulipristal acetate and P-gp substrates (e.g. dabigatran etexilate, digoxin), is not recommended (see section 4.4)."

The CHMP, having considered the data submitted, was of the opinion that the below pharmacovigilance activities in addition to the use of routine pharmacovigilance are needed to investigate further some of the safety concerns:

Description	Due date
PGL09-026. Phase III Study A Phase III, multicentre, clinical study investigating the efficacy and safety of 3 months open-label treatment with ulipristal acetate, followed by a randomised, double-blind placebo controlled period of 10 days treatment with progestin, in subjects with fibroids and heavy uterine bleeding.	Q3 2012
PGL09-027. Phase III Study extension phase A Phase III, multicentre, clinical study investigating the efficacy and safety of three successive periods of 3-month open-label ulipristal acetate treatment, each followed by ten days of double-blind treatment with progestin or placebo and a drug-free period until return of menses, in subjects with fibroids and heavy uterine bleeding.	Q1 2014
PGL10-014. Non interventional study in pre-operative treatment of moderate to severe symptoms of uterine fibroids A prospective multicenter non-interventional study of women treated with Esmya (ulipristal acetate) as pre-operative treatment of moderate to severe symptoms of uterine fibroids	Q4 2015
PGL11-020. Esmya prescription patterns in Europe A retrospective drug utilisation chart review study.	Q3 2015
PGL-W-001. Phase I study in women with mild, moderate and severe hepatic impairment	Q3 2014
Phase I DDI study with P-gP substrate	Q3 2013
A 104-week carcinogenicity study in rats and a 26-week carcinogenicity study in transgenic TgRasH2 mice	Q4 2012

The following additional risk minimisation activities were required:

- Educational material to prescribers (gynaecologists) (see Annex 11) when product made available which will include the full SmPC. In addition to the SmPC and its highlighted extracts, the "Physician's guide to prescribing" will include a detailed recommendation of endometrial thickness management with a reminder of the endometrial effect and the need to inform the pathologist that the patients was treated with Esmya if biopsy/surgical samples are send for analysis. The material will include a cover letter reminding the indication (pre-operative treatment and limited to 3 months) and posology details (treatment should not exceed 3 months); all documents will highlight treatment duration is limited to 3 months because of the absence of safety data on longer treatment than 3 months or on re-treatment. The material will also highlight the need to investigate any persistence of endometrial thickening to exclude underlying conditions.
- Educational material to pathologists (see Annex 12) when product made available in each country with a "Pathologist's guide", a USB stick or CD ROM with images of digital specimens (digital library with high resolution images) to compare histological appearances of PAEC and endometrial hyperplasia, and a copy of the SmPC.

2.8. Significance of paediatric studies

Not applicable

2.9. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

Benefits

Beneficial effects

The primary goal of ulipristal acetate treatment in the pivotal studies (PGL07-021, PGL07-022) was to reduce heavy menstrual bleeding and anaemia, decrease myoma related symptoms prior to surgery For treatment of fibroid-related bleeding and anaemia, ulipristal acetate was superior compared to placebo after 3 months of treatment and non-inferior to a GnRH-agonist.

In the active comparator-controlled trial, a reduction in size of the three largest fibroids as assessed by ultrasound was a secondary endpoint. The median 'reduction in size of the three largest myomas' (PP) was non-inferior in the ulipristal acetate groups compared to the leuprorelin treated group. The volume decrease in the pre-operative group was -25.6% in the 5 mg arm, -31.0% in the 10 mg arm and -46.6% in the leuprorelin arm. At 6 months post-treatment, fibroid volume reduction was better maintained following ulipristal acetate than following GnRH-agonist.

Uncertainty in the knowledge about the beneficial effects.

No uncertainties in the knowledge about the beneficial effects have been identified.

Risks

Unfavourable effects

The safety database includes women treated with a dose of 5 mg/day or higher up to 3 months from Studies PGL-N-0287, PGL-N-0090, PGL07-021 and PGL07-022. Complete 6-month, post-treatment clinical study reports of the pivotal phase III studies were also submitted (PGL07-021 and PGL07-022 Part B CSRs) and interim safety analysis from the ongoing Phase IIIb Study PGL09-026. The inclusion of the subjects from study PGL09-026 increases the number of patients having been exposed to at least 3 months of ulipristal acetate to the target dose of 5 mg or above to a total of 529 subjects.

The most frequently reported adverse events in the two pivotal studies were related to the reproductive system and the breast, and assessed as mild or moderate for all treatment groups.

There is no agreement on the upper limit of normal endometrial thickness in women of reproductive age, but according to the American College of Radiologists (Fleischer A.C. et all, 2007), Endometrial thickness > 16 mm has been proposed as a valid cut off for suggesting possible endometrium pathology (positive predictive value of 14% for demonstrating relevant pathology). The percentage of patients with endometrial thickness >16 mm was higher with 5 mg (11% in PGL07-021 and PGL07-022) and 10 mg (7% in PGL07-021 and 15% in PGL07-022) ulipristal acetate compared to placebo (2%) and leuprorelin (1%) at Week 13. In line with these findings are the TEAEs of endometrial hypertrophy in 3 subjects who received 10 mg/day ulipristal acetate. At Week 17 (1 month post-treatment) there was, however, no difference between the treatments in PGL07-022. Thus, the

submitted data are reassuring that the increased percentage of endometrium thickness > 16 mm is reversed 1 month post-treatment.

In the assessments of endometrial biopsies, a large variation between pathologists in the histopathologic evaluation highlights the need for further investigations. An increased number of subjects with endometrial thickness >16 mm at week 13 were noted in groups treated with ulipristal acetate compared to placebo or leuprorelin. In clinical routine, findings of "non-physiological" endometrium as well as an increased endometrial thickness might lead to further examination to exclude endometrial pathology. To address this matter, prescribers will be informed in the SmPC that increased thickening of the endometrium may occur (SmPC, Section 4.4) and that up to 15% of the patients may experience a thickening exceeding 16mm and such thickening may be investigated if persisting more than 3 months following the end of treatment and return of menstruations (SmPC, Section 5.1). Additionally, the applicant has provided an educational program to enforce this information.

Uncertainty in the knowledge about the unfavourable effects

Concerning human pharmacokinetics, the dossier contains studies for the characterisation of pharmacokinetic properties of ulipristal acetate. However, the data are limited. Two *in vivo* interaction studies are available and no studies were performed in special populations. To address this matter. prescribers will be informed in the SmPC of recommendations for patients with renal impairment, hepatic impairment and children. The applicant will also conduct a Phase I study in women with mild, moderate and severe hepatic impairment (PGL-W-001).

Non-physiological changes in the endometrium (cystic hyperplasia) have been observed with Esmya during the 3-month clinical trials. An additional 6-month post-treatment follow-up after 3 months of treatment with Esmya has been submitted. Endometrial safety has not been established beyond 3 months as no safety data are available for a treatment duration longer than 3 months, except for 9 subjects in study PGL-N-0090.

The indication has therefore been restricted to patients who are planned for surgery only. The SmPC also includes a statement in section 4.2 to limit the risk for off-label use and a contra-indication in section 4.3 for treatment beyond 3 months.

In addition to this, the applicant has agreed as part of the RMP to conduct a retrospective chart review to identify the risk for off-label use and provided a synopsis (PGL11-020). Not less than 1000 subjects will be identified and retrospectively followed-up for 12 months after 3 month treatment. The final protocol will be agreed by the CHMP.

The proposed educational program for gynaecologists and pathologists has been revised and is considered acceptable. The proposed survey is aimed to investigate the knowledge of ulipristal acetate among all prescribers and pathologists who received the educational program. The educational program, in combination with the proposed prescription pattern study are considered sufficient and will provide appropriate measures on reducing the risk of inappropriate management of endometrium thickening (unnecessary interventions and treatments), inappropriate diagnosis of endometrial hyperplasia (mistaken as PAEC), delayed diagnosis of atypical endometrial hyperplasia or adenocarcinoma, and long term treatment with ulipristal acetate.

Benefit-risk balance

Importance of favourable and unfavourable effects

A clinically significant reduction in bleeding and anaemia were demonstrated when ulipristal acetate was compared to placebo, and non-inferior to the comparator GnRH-agonist with a more rapid effect when given for a period of three months. A significant reduction in fibroid size is considered adequately shown. For pre-operative treatment, the clinical relevance of Esmya is justified.

Significant changes in endometrial thickness may, however, occur with non-physiological changes and increase in thickness. The increased percentage of endometrium thickness > 16 mm is reversed after discontinuation. The incidence of endometrial hyperplasia was very low (1 case) and no different to controls (one case with placebo and one case with GnRH-agonist).

Endometrial data at week 38 in Study PGL07-021 and Study PGL07-022 are reassuring regarding diagnosis of malignant changes, cellular atypia or other findings of concern in the ulipristal acetate treatment groups. The incidence of PAEC at week 38 (6 months after end of treatment) was similar to that observed at screening. The short-term safety data after 3 months of treatment with Esmya do not show an increased risk for malignant changes in the endometrium (studies PGL07-021, PGL07-022 and PGL09-026). Further data regarding the carcinogenic potential of ulipristal acetate will be provided by two ongoing non-clinical carcinogenicity studies.

Duration of treatment was restricted to 3 months, except for 9 subjects. It is therefore unknown whether the non-physiological changes observed during treatment might lead to endometrial pathology if treatment is continued beyond 3 months of treatment. As a consequence, treatment duration has been limited to 3 months.

Benefit-risk balance

The clinical efficacy has been adequately established and there are no major safety concerns. In conclusion, the B/R balance of Esmya for the pre-operative treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age is positive. The duration of treatment is limited to 3 months.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Esmya is positive for the pre-operative treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age. The duration of treatment is limited to 3 months.

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Conditions and requirements of the Marketing Authorisation

Risk Management System and PSUR cycle

The MAH must ensure that the system of pharmacovigilance, presented in Module 1.8.1 of the marketing authorisation, is in place and functioning before and whilst the product is on the market.

The MAH shall perform the pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in version 7 of the Risk Management Plan (RMP) presented in Module 1.8.2 of the marketing authorisation and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted:

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- at the request of the EMA

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Prior to launch of the product in each Member State, the Marketing Authorisation Holder shall agree the content and format of the educational material with the national competent authority.

The Marketing Authorisation Holder (MAH) shall ensure that, at launch and thereafter, all prescribers of Esmya and pathologists who review samples from Esmya-treated patients are provided with educational material.

The educational material shall consist of the following:

- Educational material for prescribers (gynaecologists) which contains:
    - Cover letter
    - SmPC
    - Physician's guide to prescribing Esmya
- Educational material for pathologists which contains
    - Pathologist's guide
    - USB stick or CD ROM with images of digital specimens (digital library with high resolution images).
    - SmPC

The educational material shall contain the following key elements:

<u>Physician's guide to prescribing</u>

- detailed recommendations for management of endometrial thickening
- reminder of the effect of ulipristal acetate on the endometrium

- the need to inform the pathologist that patients were treated with Esmya if biopsy/surgical samples are to be sent for analysis.
- the indication: pre-operative treatment limited to 3 months
- the contraindications of pregnancy and breastfeeding, genital bleeding of unknown aetiology or for reasons other than uterine fibroids, and uterine, cervical, ovarian or breast cancer
- absence of safety data for treatment longer than 3 months and for re-treatment
- the need to investigate as per usual clinical practice persistence of endometrial thickening following treatment discontinuation and return of menstruation to exclude underlying conditions.

Educational material for pathologists

- key effects of Esmya on Progesterone Receptor Modulator Associated Endometrial Changes (PAEC) and how they differ from those of unopposed oestrogen
- the differential diagnosis between PAEC, unopposed oestrogen and endometrial hyperplasia

Obligation to complete post-authorisation measures

Not applicable

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

The Member States should ensure that all conditions or restrictions with regard to the safe and effective use of the medicinal product as described below are implemented:

Prior to launch of the product in each Member State, the Marketing Authorisation Holder shall agree the content and format of the educational material with the national competent authority.

The Marketing Authorisation Holder (MAH) shall ensure that, at launch and thereafter, all prescribers of Esmya and pathologists who review samples from Esmya-treated patients are provided with educational material.

The educational material shall consist of the following:

- Educational material for prescribers (gynaecologists) which contains:
  - Cover letter
  - SmPC
  - Physician's guide to prescribing Esmya
- Educational material for pathologists which contains
  - Pathologist's guide
  - USB stick or CD ROM with images of digital specimens (digital library with high resolution images).
  - SmPC

The educational material shall contain the following key elements:

Physician's guide to prescribing

- detailed recommendations for management of endometrial thickening
- reminder of the effect of ulipristal acetate on the endometrium
- the need to inform the pathologist that patients were treated with Esmya if biopsy/surgical samples are to be sent for analysis.
- the indication: pre-operative treatment limited to 3 months
- the contraindications of pregnancy and breastfeeding, genital bleeding of unknown aetiology or for reasons other than uterine fibroids, and uterine, cervical, ovarian or breast cancer.
- absence of safety data for treatment longer than 3 months and for re-treatment
- the need to investigate as per usual clinical practice persistence of endometrial thickening following treatment discontinuation and return of menstruation to exclude underlying conditions.

Educational material for pathologists

- key effects of Esmya on Progesterone Receptor Modulator Associated Endometrial Changes (PAEC) and how they differ from those of unopposed oestrogen
- the differential diagnosis between PAEC, unopposed oestrogen and endometrial hyperplasia

Additional data / market exclusivity

Furthermore, the CHMP reviewed the data submitted by PregLem France SAS, taking into account the provisions of Article 14(11) of Regulation (EC) No 726/2004 and considers by consensus that the new therapeutic indication brings significant clinical benefit in comparison with existing therapies.