GEDEON RICHTER preglem

PGL14-001 (PREMIUM): Study Protocol amended (version 1.3)

PASS Information

Title	A prospective, multi-national, multicentre, non-interventional study to evaluate the long term safety of Esmya, in particular the endometrial safety, and the current prescription and management patterns of Esmya in a long term treatment setting.
Version identifier	1.3
Date of last version of protocol	21 August 2018
EU PAS register number	EUPAS16792
Active Substance	Pharmacotherapeutic group: Sex hormones and modulators of the genital system, progesterone receptor modulators. ATC code: G03XB02. Ulipristal acetate
Medicinal product	Esmya 5 mg tablets
Product reference	EU/1/12/750/001-005
Procedure number	EMEA/H/C/002041
Marketing authorisation holder	Gedeon Richter Plc.
Joint PASS	No
Research question and objectives	The specific objectives of the study are to: • Assess the long term safety, including endometrial safety, of Esmya in standard medical practice • Assess prescription patterns of Esmya in standard medical practice Exploratory objective: • Assess patients' quality of life in a long-term treatment setting.
Countries of study	Approximately 15 EU countries including at least UK, Germany, France and Spain. (Full country list to be finalised)
Author	Kerry Ferrero, Medical Affairs Manager, Medical Affairs PregLem S.A, member of Gedeon Richter group.

Marketing authorisation holder

Marketing Authorisation Holder (MAH)	Gedeon Richter Plc. Gyömrői út 19-21. 1103 Budapest Hungary
MAH contact person	Daniela Ciobanu, Regulatory Affairs & Quality Management Manager PregLem S.A., member of Gedeon Richter group. Route de Frontenex 41A 1207 Geneva, Switzerland Phone: +41 22 884 03 56

SIGNATURE PAGE

Approved by:

Sponsor:

PregLem SA, member of Gedeon Richter Group, Route de Frontenex 41A, 1207 Geneva, Switzerland

[redacted]

28 August 2018

Date of signature

Kerry Ferrero

[redacted]

28 August 2018

Date of signature

Signature
Pablo Arriagada M.D.
VP, Medical Affairs
(Medical Responsible)

INVESTIGATOR ENDORSEMENT PAGE

I, the undersigned, am responsible for the conduct of the study at this site and agree to the following:

- I understand and will conduct the study according to the protocol, any approved protocol amendments and all applicable regulatory authority requirements and national laws.
- I have read and understand fully the approved product label for ESMYA.
- I have sufficient time and an adequate number of qualified staff to conduct and complete the study properly and safely.
- I will ensure that all staff at my site(s) who are involved in the study conduct are adequately trained regarding the protocol and their responsibilities. In the case of delegating any of my study responsibilities I will provide the Sponsor with a Delegation of Activities certificate.

Signature | Date of signature

[Insert Name, academic qualifications]

[Insert Position (title)]
[Insert Address of Institution]

1 TABLE OF CONTENTS

1 TABLE OF CONTENTS

TABLE OF TABLES

2 LIST OF ABBREVIATIONS

AE	Adverse Event
ADR	Adverse Drug Reaction
ATC	Anatomical Therapeutic Chemical Classification
CI	Confidence Interval
CGI-I	Clinical Global Impression Index
cm	Centimetres
CRA	Clinical Research Associate
CRO	Clinical Research Organisation
EDC	Electronic Data Capture
eCRF	Electronic Case Report Form
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EQ-5D	Questionnaire for measuring Health outcome from the EuroQol group
EU	European Union
FPI	First Patient In
GnRH	Gonadatropin Releasing Hormone
GRRO	Gedeon Richter Romania
HCP	Health Care Professional
HRQL	Health Related Quality of Life
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ITT	Intention to Treat
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligrams
N	Number of Patients
PAEC	Progesterone receptor modulator Associated Endometrial Changes
PAS	Post Authorisation Study
PASS	Post Authorisation Safety Study
PRO	Patient Reported Outcome
QoL	Quality of Life
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Systems
SmPC	Summary of Product Characteristics
SPRM	Selective Progesterone Receptor Modulator
UK	United Kingdom
UFS-QOL	Uterine Fibroid Symptom and Health-Related Quality of Life Questionnaire
UPA	Ulipristal Acetate
VAS	Visual Analogue Scale

3 RESPONSIBLE PARTIES

The list of main responsible parties involved in the study is provided in Table 1.

The list of all investigators who will be involved in the study will be kept as a stand-alone document as listed in Annex 1.

Table 1 Responsible Parties

Role	Responsible person	Address
Main author of the protocol	Kerry Ferrero BSc (HONS) Medical Affairs Manager Medical Affairs	PregLem S.A. (member of Gedeon Richter group) Route de Frontenex 41A 1207 Geneva, Switzerland Email kerry.ferrero@preglem.com Ph +41 22 884 03 58 Fx + 41 22 884 03 51
Medical Responsible of the protocol	Pablo Arriagada M.D. Vice President Medical Affairs	PregLem S.A. (member of Gedeon Richter group) Route de Frontenex 41A 1207 Geneva, Switzerland Email pablo.arriagada@preglem.com Ph +41 22 884 03 55 Fx + 41 22 884 03 49
Principal / Co-Ordinating Investigator (s)	To be Confirmed	To be Confirmed
Clinical Research Organisation (CRO) for Conduct of the Study	ICON	ICON Clinical Research Limited South County Business Park Leopardstown Dublin 18 Ireland

4 ABSTRACT

Title: A prospective, multi-national, multicentre, non-interventional study to evaluate the long-term safety of Esmya, in particular the endometrial safety, and the current prescription and management patterns of Esmya (PREMIUM).

Release date: Date

Main Author: Kerry Ferrero, Medical Affairs Manager, Medical Affairs, PregLem S.A, member of Gedeon Richter Group.

Rationale and background:

Uterine leiomyomas, or fibroids, are the most common benign uterine tumours and they occur in about 20-40% of women of reproductive age [(1)]. In addition to adversely affecting quality of life (QoL) and fertility, fibroids can cause heavy menstrual bleeding, pelvic pressure and pain, dysmenorrhea and chronic fatigue [(2)]. Surgical and radiological interventions still predominate as treatment measures [(3)]. Until recently, options for medical therapy were limited to pre-operative reduction of symptoms related to uterine bleeding and fibroid size. [(4-5)]. However, current therapies now include intramuscular/subcutaneous gonadotropin releasing hormone (GnRH) agonists or Esmya 5 mg tablets. Ulipristal acetate is indicated for one treatment course of pre-operative treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age.

Ulipristal acetate is indicated for intermittent treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age who are not eligible for surgery

Esmya is a selective progesterone receptor modulator (SPRM) whose main pharmacodynamic property is to reversibly block the progesterone receptor in its target tissues (uterus, cervix, ovaries, and hypothalamus). It acts as a potent, orally active progesterone receptor modulator. Its pharmacokinetic properties support once daily dosing that potently modulate progesterone-receptor activity, showing proapoptotic/antiproliferative effects on fibroid cells [(8-10)].

As the SPRM mechanism of action (MoA) is mainly described as progesterone receptor antagonism, the hypothetical risk that its administration results in a situation comparable to un-opposed oestrogen exposure has been assessed and debated by experts in the literature.

However, the SPRM mechanism of action is different from an unopposed oestrogen effect and in vitro and in vivo studies have shown that SPRMs are not exclusively pure progesterone receptor antagonists. They also exert anti-oestrogenic effects through either a partial progesterone receptor agonist activity and/or through up-regulation of the androgen receptor response. These SPRM effects are evidenced by the observed dose-dependent suppression of oestrogen-induced mitotic activity in target tissues. They consequently display a mixed agonist/antagonist activity which is additionally combined with an anti-proliferative effect on the endometrium [(11 ; 12)].

Esmya has been shown to reduce fibroid volume and to control uterine bleeding either in short term pre-operative use (1 course of 3 months) or long term use (repeated intermittent 3-month treatment courses). After a 3-month course treatment cessation, return of menstruation usually occurs within four to five weeks but fibroid volume reduction can be sustained for up to six months. In addition, treatment with UPA improved quality of life, reduced fibroid-associated pain and revealed no safety concerns [(13; 14)]. SPRMs including Esmya have a specific pharmacodynamic effect on the endometrium, and distinctive histological features occur in many patients who receive treatment. These histological patterns are benign, non-physiological, non-proliferative, histological features of the endometrium termed Progesterone receptor modulator Associated Endometrial Changes (PAEC) [(15-17)]. These changes spontaneously reverse over a few weeks to months following cessation of the three-month UPA treatment [(6; 7; 18)]. The efficacy and safety of UPA for treating symptomatic uterine fibroids has been documented in a number of clinical studies. Two Phase III studies have been performed to assess efficacy and safety of long term (repeated intermittent) use of UPA. The first Phase III clinical study (PGL09-027; PEARL III Extension) evaluating the long-term repeated use of UPA 10 mg daily for four 12 week consecutive treatment courses has demonstrated effective control of uterine bleeding and pain, fibroid volume reduction and restore of Quality of Life (QoL) [(19)].

In addition, the sponsor has conducted a second long term use Phase III study (PGL11-006; PEARL IV) to evaluate the efficacy and safety of up to 4 repeated 12 week courses of daily 5 mg or daily 10 mg doses of UPA. During Part I of the study (2 courses), 62% and 73% of patients in the 5 mg and 10 mg UPA groups

respectively achieved amenorrhea at the end of both treatment courses. The proportions of patients with controlled bleeding at the end of treatment course 2 was >87% in both groups. Median reduction from baseline to end of treatment course 2 in fibroid volume was 54% and 58% for patients receiving 5 mg and 10 mg UPA respectively. During the Part II of the study (4 courses), 49% and 60% of patients in the 5 mg and 10 mg UPA groups respectively achieved amenorrhea at the end of all four treatment courses. The proportions of patients with controlled bleeding at the end of treatment course 4 was >73% in both groups. Median reduction from baseline to end of treatment course 4 in fibroid volume was 72% and 73% for patients receiving 5 mg and 10 mg UPA respectively. Pain and quality of life improved in both treatment groups with 2 and 4 courses. Ulipristal acetate at both doses was well tolerated with less than 5% patients discontinuing treatment due to adverse events. These results showed that repeated 12-week courses of oral UPA 5 mg and 10 mg once daily effectively control bleeding and pain, reduce fibroid volume and restore quality of life in patients with symptomatic fibroids [20].

To date, no data on Esmya in standard medical practice for the long term use is available.

The purpose of this observational study is to evaluate the long term safety of Esmya, in particular the endometrial safety, in standard medical practice and the current prescription and management patterns of Esmya in a long term treatment setting.

Due to the observational design, this study will allow collection of data on long term safety including symptoms, procedures (if any) and diagnosis related to endometrial safety, including the occurrence of endometrial hyperplasia and adenocarcinoma and the number of treatment courses and duration of the treatment courses. In addition, as an exploratory endpoint, study will collect Quality of Life data.

Research question and objectives

The specific objectives of the study are to:

- Assess the long term safety, including endometrial safety, of Esmya in standard medical practice
- Assess prescription patterns of Esmya in standard medical practice in long term treatment setting

Study design:

This is a multi-centre, multinational, prospective, non-interventional study in females with a diagnosis of moderate to severe uterine fibroids, and for whom a treatment with Esmya in a long term manner is planned, and in subjects who were previously exposed to UPA in the long term Phase III studies. It is planned to enrol approximately 1,500 patients. Consecutive, eligible, patients will be invited to enrol from approximately 100-150 European Union (EU) clinical practice sites in approximately 15 countries. Patients will be followed for an observation period of 60 months (5 years) from treatment start. Investigators are to manage and treat patients according to their standard medical practice.

Population:

The target study population will include women with moderate to severe symptoms of uterine fibroids, and for whom a treatment with Esmya in a long term manner is planned, and subjects who were previously exposed to UPA 5 or 10 mg in Long Term Phase III clinical trials PGL09-027 (PEARL III extension; including patients of PGL11-024 (PEARL extension 2)), or PGL11-006 (PEARL IV).

Variables and data sources:

All data for variables/outcomes and EQ-5D questionnaires will be collected at each patient visit and entered into web-based Electronic Data Capture (EDC) forms by the site staff. This data originates from the clinical records used by each site according to local practice and their local data collection standards. Any surgical or other invasive gynaecological interventions during the study period are to be collected, where possible. Clinical evaluations according to standard medical practice will include, but are not limited to: gynaecological examination, ultrasound evaluation (transvaginal, abdominal), biopsies etc.

Study Size:

Given the descriptive nature of the study, the target sample size is not based on any formal test of hypotheses. A sample of 1,500 patients is felt to be a strong basis to assess safety and will provide sufficient data to perform analyses for outcomes related to long-term treatment with Esmya.

Data Analysis:

The majority of statistical analyses will be descriptive, reporting patient counts, means, standard deviations, medians, minima, and maxima for continuous variables (e.g., age and duration of symptomatic uterine fibroids) and frequencies and percentages for categorical variables (e.g., disease symptoms, prescription pattern, diagnostic test results). Two-sided 95% confidence intervals will be estimated as appropriate and reported along with p-values to facilitate the interpretation of the significance of the findings. These findings will be compared to published epidemiological data on pre-menopausal women with abnormal uterine bleeding (AUB), where available.

Baseline data (i.e. data collected prior to the first administration of Esmya), including relevant demographic characteristics will be summarised for all treated subjects.

All other endpoints will be summarised by visit/assessment, where available.

All subjects who receive at least one dose of either medicinal product (Esmya) or previously received UPA 5 or 10 mg in the long term Phase III trials will be included in the analysis population (i.e. Safety / Intention to Treat).

No data will be imputed, only reported values will be used for the purpose of the analysis.

In addition to the main analysis population, sub-group analyses will be carried out on:

- All patients who completed at least 4 courses within the study period (60 months)
- All patients who had any individual treatment course with a duration > 3 months (i.e. continuous treatment)
- All patients who were previously treated in the long term Phase III studies.

Milestones:
A progress report will be carried out on a yearly basis, from date of First Patient In (FPI), to report progress of the study and results on major endpoints, where appropriate. A final report will be generated at the end of the study.

5 AMENDMENTS AND UPDATES

VERSION HISTORY

Amendment Number	Amendment Date	Country-Specific*	Amended Protocol Number
01	08 October 2015	Introduction of the EQ-5D questionnaire in the following countries: Austria, Belgium, Denmark, France, Germany, Hungary, Italy, Poland, Portugal, Romania, Spain, Sweden and UK	1.2

		(*Pending competent authority approval in: Czech Republic, Latvia, Lithuania and Netherlands)	
02	18 February 2016	*Further explanation of endpoints to be assessed, applicable for country: Spain	1.2 &1.3
03	12 May 2017	*Further explanation of exclusion criteria to be assessed, applicable for country: France	1.2
04	21 August 2018	General Amendment to Protocol 1.2 12 October 2015: All countries (Including France): Changes to Inclusion and Exclusion criteria following changes to SmPC. Addition of Liver monitoring measures to align with new changes to the SmPC. Administrative changes (Competent authority approval for EQ-5D received in: Czech Republic, Latvia, Lithuania and Netherlands)	1.3

6 MILESTONES

The project planned timelines and actual due dates of the study are summarised in **Table 2**

Table 2 Project Milestones

Activity	Planned Date *
Start of Data Collection	Dec 2015
End of Data Collection	Dec 2022
Study Progress Report 1 to 7	Q4 2016, 2017, 2018, 2019, 2020, 2021, 2022
Registration in the EU PAS Register	20.12.2016
Final Report of Study Results	Q1 2023

* All given dates / timelines are tentative and could be subject to further changes.

7 RATIONALE AND BACKGROUND

Uterine leiomyomas, or fibroids, are the most common benign uterine tumours and they occur in about 20-40% of women of reproductive age [(1)]. In addition to adversely affecting quality of life (QoL) and fertility, fibroids can cause heavy menstrual bleeding, pelvic pressure and pain, dysmenorrhea and chronic fatigue [(2)].
Surgical and radiological interventions still predominate as treatment measures [(3)]. Until recently, options for medical therapy were limited to pre-operative reduction of symptoms related to uterine bleeding and fibroid size [(4-5)]. However, current therapies now include intramuscular/subcutaneous gonadotropin releasing hormone (GnRH) agonists or Esmya 5 mg tablets.

Ulipristal acetate is indicated for one treatment course of pre-operative treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age.

Ulipristal acetate is indicated for intermittent treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age who are not eligible for surgery

Esmya is a selective progesterone receptor modulator (SPRM) whose main pharmacodynamic property is to reversibly block the progesterone receptor in its target tissues (uterus, cervix, ovaries, and hypothalamus). It acts as a potent, orally active progesterone receptor modulator. Its pharmacokinetic properties support once daily dosing that potently modulate progesterone-receptor activity, showing proapoptotic/antiproliferative effects on fibroid cells [(8-10)].
As the SPRM mechanism of action (MoA) is mainly described as a progesterone receptor antagonism, the hypothetical risk that its administration results in a situation comparable to un-opposed oestrogen exposure has been assessed and debated by experts in the literature. However, the SPRM mechanism of action is different from an unopposed oestrogen effect and in vitro and in vivo studies have shown that SPRMs are not exclusively pure progesterone receptor antagonists. They also exert anti-oestrogenic effects through either a partial progesterone receptor agonist activity and/or through up-regulation of the androgen receptor response. These SPRM effects are evidenced by the observed dose-dependent

suppression of oestrogen-induced mitotic activity in target tissues. They consequently display a mixed agonist/antagonist activity which is additionally combined with an anti-proliferative effect on the endometrium [11; 12].
Esmya has been shown to reduce fibroid volume and to control uterine bleeding either in short term pre-operative use (1 course of 3 months) or long term use (repeated intermittent 3-month treatment courses).
After a 3-month course treatment cessation, return of menstruation usually occurs within four to five weeks but fibroid volume reduction can be sustained for up to six months. In addition, treatment with UPA improved quality of life, reduced fibroid-associated pain and revealed no safety concerns [13; 14]. SPRMs including Esmya have a specific pharmacodynamic effect on the endometrium, and distinctive histological features occur in many patients who receive treatment. These histological patterns are benign, non-physiological, non-proliferative, histological features of the endometrium termed Progesterone receptor modulator Associated Endometrial Changes (PAEC) [15-17]. These changes spontaneously reverse over a few weeks to months following cessation of the three-month UPA treatment [6; 7; 18]. The efficacy and safety of UPA for treating symptomatic uterine fibroids has been documented in a number of clinical studies. Two Phase III studies have been performed to assess efficacy and safety of long term (repeated intermittent) use of UPA. The first Phase III clinical study (PGL09-027; PEARL III Extension) evaluating the long-term repeated use of UPA 10 mg daily for four 12 week consecutive treatment courses has demonstrated effective control of uterine bleeding and pain, fibroid volume reduction and restore of Quality of Life (QoL) [19].
In addition, the sponsor has conducted a second long term use Phase III study (PGL11-006; PEARL IV) to evaluate the efficacy and safety of up to 4 repeated 12 week courses of daily 5 mg or daily 10 mg doses of UPA. During Part I of the study (2 courses), 62% and 73% of patients in the 5 mg and 10 mg UPA groups respectively achieved amenorrhea at the end of both treatment courses. The proportions of patients with controlled bleeding at the end of treatment course 2 was >87% in both groups. Median reduction from baseline to end of treatment course 2 in fibroid volume was 54% and 58% for patients receiving 5 mg and 10 mg UPA respectively. During the Part II of the study (4 courses), 49% and 60% of patients in the 5 mg and 10 mg UPA groups respectively achieved amenorrhea at the end of both treatment courses. The proportions of patients with controlled bleeding at the end of treatment course 4 was >73% in both groups. Median reduction from baseline to end of treatment course 4 in fibroid volume was 72% and 73% for patients receiving 5 mg and 10 mg UPA respectively. Pain and quality of life improved in both treatment groups with 2 and 4 courses. Ulipristal acetate at both doses was well tolerated with less than 5% patients discontinuing treatment due to adverse events. These results showed that repeated 12-week courses of oral UPA 5 mg and 10 mg once daily effectively control bleeding and pain, reduce fibroid volume and restore quality of life in patients with symptomatic fibroids [20].
To date, no data on Esmya in standard medical practice for the long term use is available. The purpose of this observational study is study to evaluate the long term safety of Esmya, in particular the endometrial safety, in standard medical practice and the current prescription and management patterns of Esmya in a long term treatment setting.
Due to the observational design this study will allow collection of data on long term safety including symptoms, procedures (if any) and diagnosis related to endometrial safety, including the occurrence of endometrial hyperplasia and adenocarcinoma and the number of treatment courses and duration of the treatment courses.

8 RESEARCH QUESTION AND OBJECTIVES

The purpose of this observational study is to evaluate the long term safety of Esmya, in particular the endometrial safety, and the current prescription and management patterns of Esmya in a long term treatment setting.

The specific objectives of the study are to:

- Assess the long term safety, including endometrial safety, of Esmya in standard medical practice
- Assess prescription patterns of Esmya in standard medical in long term treatment setting.

The following endpoints will be assessed during the study period:

- Collect/follow symptoms related to long term safety, including endometrial safety:
    - evaluate the occurrence of and describe any symptoms related to endometrial safety e.g. unexpected, altered or abnormal bleeding patterns and/or the treatment/interventions performed
    - evaluate the frequency of findings of endometrial thickening >16 mm and document any follow-up investigations, and/or treatment/interventions performed
    - evaluate the frequency of diagnosis of endometrial hyperplasia and any follow-up investigations and/or, treatments/interventions performed and the rate at which this diagnosis is confirmed by second opinion, where available
    - evaluate any reports of adenocarcinoma and their outcome, where available
    - evaluate the occurrence of and describe any symptoms related to hepatic safety/liver laboratory values and interventions, where available, *with focus on drug-induced liver injury*
    - all gynaecological Adverse Events considered as related or not related to Esmya,
    - Serious Adverse Events (SAEs) considered as related or not related to Esmya,
    - non-serious Adverse Drug Reactions (ADRs),
    - Adverse Events (AEs) leading to Esmya treatment discontinuation
    - all pregnancies occurring from treatment start until the end of patient follow-up.
- Collect prescription patterns of Esmya in order to clarify the extent and nature of long term exposure:
    - number of treatment courses of Esmya
    - the duration of treatment with Esmya during each treatment course and overall
    - Collect the demographic characteristics of patients treated with Esmya
    - the demographic characteristics of patients treated with Esmya e.g. age, BMI, ethnicity

- the number and type of concomitant treatment(s) during the study period.

In addition, in an exploratory manner, Quality of Life data will be collected:

Exploratory objective:
Assess patients' quality of life in a long-term treatment setting.

Exploratory endpoint:

- Collect EQ-5D questionnaires from the patients at the enrolment visit and each visit until the end of the study.

9 RESEARCH METHODS

9.1 Study Design

This is a multi-centre, multinational, prospective, non-interventional study in females with a diagnosis of moderate to severe uterine fibroids, and for whom a treatment with Esmya in a long term manner is planned, and in subjects who were previously exposed to UPA 5 or 10 mg in the long term Phase III studies. It is planned to enrol approximately 1,500 patients. Consecutive, eligible, patients will be invited to enrol from approximately 100-150 European Union (EU) clinical practice sites in approximately 15 countries. Patients will be followed for an observation period of 60 months from treatment start. No specific diagnostic tests or treatments or pharmacologic agents after Esmya initiation are required as part of the study, however all procedures or interventions performed will be collected. Physicians are to manage and treat patients according to their standard medical practice.

Study visits will occur at enrolment, and will then be followed by visits according to their standard medical practice of the physician. Standard medical practice is assumed to include, at minimum, visits approximately every 8 months (i.e. after approximately 2 treatment courses). However, requested study data will be collected, when available, at all visits, regardless of the time since the last visit. The study will end, for each patient, 60 months from the date of start of treatment.

9.2 Setting

9.2.1 Patients

The target study population will include women with moderate to severe symptoms of uterine fibroids, and for whom a treatment with Esmya in a long term manner is planned.

In addition, subjects who were previously exposed to UPA 5 or 10 mg in long term Phase III clinical trials PGL09-027 (PEARL III extension; including patients of PGL11-024 (PEARL extension 2)), or PGL11-006 (PEARL IV) will be contacted and followed-up. This will serve to complement the data which will be obtained prospectively from newly treated patients and maximise long term follow-up information.

Patients who meet the inclusion criteria will be invited to participate in the study. Sites will be asked to complete a list of all eligible patients who are invited to participate, and to indicate those patients who decline to participate.

9.2.1.1 Inclusion Criteria and Exclusion Criteria

To be eligible for inclusion into this study, the subjects must **fulfil all** of the following criteria:

- Adult women of reproductive age with a diagnosis of moderate to severe symptoms of uterine fibroids who are not eligible for surgery and for whom an intermittent treatment with Esmya in a long term manner (at least 2 courses), is planned ; or subjects who were exposed to UPA 5 or 10 mg during long term Phase III trials PGL09-027 (PEARL III extension, including patients (PEARL extension 2)) or PGL11-006 (PEARL IV), and
- Patient is willing and able to attend visits which are scheduled by her treating physician for the regular follow-up, provide the required medical data, and
- Patient has personally signed and dated the informed consent document indicating that she has been informed of all pertinent aspects of the study.

To be eligible for inclusion in this study the subjects must **not** meet any of the following criteria at the time of inclusion:

- Patient is prescribed Esmya for pre-operative treatment
- Patient has a contraindication to receive Esmya as per SmPC
- Patient is using an investigational drug/therapy or has discontinued the use of an investigational drug/therapy within 30 days prior to study enrolment,
- Patient has hypersensitivity to the active substance of Esmya or to one of its excipients,
- Not applicable to long term phase III previous subjects who are not planning to receive Esmya during this study:
  - Patient is pregnant or plans to become pregnant within the next 12 months from treatment start,
  - Patient is breastfeeding,

- Patient has genital bleeding of unknown aetiology or not due to uterine fibroids,
- Patient has been diagnosed with uterine, cervical, ovarian or breast cancer.

9.2.1.2 Discontinuation of Patients from the Study

Patients may withdraw/discontinue from the study at any time at their own request. They may also be withdrawn at any time at the discretion of the investigator or by the sponsor for administrative reasons (e.g. discontinuation of a site), but may continue treatment according to medical practice outside of the study.

In addition, newly prescribed patients who have a period of > 3 months from study enrolment to start date of first course of Esmya will be withdrawn from the study, but may continue treatment according to medical practice outside of the study.

Patients who inform their physician of their intent to withdraw from the study prior to any visit will be asked a brief series of questions to document the reason for withdrawal, and to collect the following information:

- Esmya treatment status (discontinued, continuing under the care of another physician)
- Reason for discontinuation, if applicable
- Occurrence of SAEs, gynaecological AE's, ADRs, AEs leading to Esmya discontinuation (irrespective of seriousness and causal relationship).

If the patient withdraws from the study no additional data will be collected beyond the withdrawal visit or phone interview. The sponsor may retain and continue to use any data collected before withdrawal of consent in accordance with the original patient consent form.

9.2.1.3 Patient Follow up

Patients will be followed for 60 months from treatment start or from previous Long Term Phase III enrollment. If a patient does not return for a follow-up visit(s), by the end of the 60 month period, the investigator (or designee) will be asked to attempt to contact the patient.

Sites will be asked to make at least 4 attempts to contact patients who have missed a follow-up visit. The attempts will be made at various times of the day and on different days of the week over a 4 week period. Patients who cannot be contacted after 4 documented attempts over a 4 week period will be considered lost to follow-up.

If contact is made the following information will be collected where possible:

- whether the patient is continuing Esmya treatment
- reason for withdrawal, if withdrawn, e.g., lack of interest, moving, switching Health Care Professional (HCP), adverse event
- any SAEs, gynaecological Adverse Events and Adverse Events considered to be related to Esmya or Adverse Events leading to Esmya treatment discontinuation.

Subsequently, the end of study form will be completed.

9.3 Variables

9.3.1 Baseline Parameters

At Visit 1, the investigator (or designee) will explain and review the study with the patient and invite her to participate. Once written informed consent has been obtained, the investigator (or designee) will collect specified study information (including for previous subjects of Long Term phase III trials their baseline data in these trials). The following data will be collected, where information is available:

- patient demographic characteristics, including age, race, weight, BMI
- medical history unrelated to OB/GYN
- vital signs
- OB/GYN medical history, including any previous medical treatment or surgery for uterine fibroids
- gynaecological examination results (including TVUS or biopsies and any results on endometrial thickening or endometrial findings, where available)
- date and method of diagnosis for uterine fibroids
- liver laboratory values and interventions
- current symptoms, including bleeding patterns
- current treatment plan
- pregnancy history and urine pregnancy test (where applicable)
- concomitant medications (coded according to WHO Drug Dictionary)
- review of all inclusion and exclusion criteria.
- record EQ-5D

The Schedule of Assessments at each visit during the study is provided in Table 3.

Table 3 Assessment Schedule

	Visit 1 Study Enrolment	Study Visits [1]
CLINICAL ASSESSMENTS [1]		
Signed Informed Consent	X	
Inclusion/Exclusion Criteria	X	
Demographics (e.g. age, weight, ethnicity)	X	
Vital signs	X	X
Medical History (unrelated to OB/GYN)	X[3]	
OB/GYN History (incl. fibroids and previous surgery)	X[3]	
Gynaecological Examination results (incl. Breast examination) & TVUS and biopsies as appropriate	X[3]	X
Bleeding Patterns	X[3]	X

EQ-5D Questionnaire	X	X
Diagnosis method (and date) of Uterine Fibroids	X	
Liver Safety Monitoring/Liver tests	**X**	**X**
Esmya Start and/or Stop dates		X
Current treatment plan	X (for inclusion)	X
Performed surgery, if any	X[3]	X
Urine pregnancy test, if available	X	
Concomitant medication	X	X
Adverse event monitoring		X
End of study form [2]		X

[1] According to standard medical practice, when available

[2] End of Study Form will be collected only at end of study assessment

[3] All data available from the end of the long term Phase III studies to Visit 1 for the subjects who were previously exposed to UPA 5 or 10 mg in the Phase III studies

The following assessments will be carried out at each visit, according to standard medical practice.

9.3.2 Endometrial Parameters

In the frame of repeated intermittent treatment, the SmPC recommends the following:

- In case of repeated intermittent treatment, periodic monitoring of the endometrium is recommended. This includes annual ultrasound to be performed after resumption of menstruation during off-treatment period. In case of persistent thickening of the endometrium and/or altered bleeding such as inter-menstrual bleeding, investigation including endometrial biopsy should be performed in order to exclude other underlying conditions.
- In case of hyperplasia (without atypia), monitoring as per usual clinical practice (e.g. a follow-up control 3 months later) would be recommended. In case of atypical hyperplasia, investigation and management as per usual clinical practice should apply.
- In addition, during repeated intermittent treatment, in case of an altered persistent or unexpected bleeding pattern, such as inter-menstrual bleeding, investigation of the endometrium including endometrial biopsy should be performed in order to exclude other underlying conditions.

Therefore, the above procedures/investigations are likely to take place and study will collect all results from test performed including but not limited to ultrasound and biopsies.

In this study, if a diagnosis of endometrial hyperplasia (simple, complex or atypical) or adenocarcinoma is made, whether resulting from endometrium biopsy or histo-pathology examination of the uterus after hysterectomy, the investigator should ask to receive

pathology slides. If obtained, these slides should be sent for review by an independent expert pathologist, provided by the Sponsor.

9.3.3 Hepatic Parameters

The SmPC recommends the following:

During the post-marketing experience, cases of liver injury and hepatic failure were reported.

Liver function tests must be performed before starting treatment. Treatment must not be initiated if transaminases (alanine transaminase (ALT) or aspartate aminotransferase (AST)) exceed 2 x ULN (isolated or in combination with bilirubin >2 x ULN).

During treatment, liver function tests must be performed monthly during the first 2 treatment courses. For further treatment courses, liver function must be tested once before each new treatment course and when clinically indicated.

If a patient during treatment shows signs or symptoms compatible with liver injury (fatigue, asthenia, nausea, vomiting, right hypochondrial pain, anorexia, jaundice), treatment should be stopped and the patient should be investigated immediately, and liver function tests performed.

Patients who develop transaminase levels (ALT or AST) > 3 times the upper limit of normal during treatment should stop treatment and be closely monitored.

In addition liver testing should be performed 2- 4 weeks after treatment has stopped.

9.3.4 Treatment Plan

At each visit the investigator will report, if applicable, any changes in the treatment plan for fibroids. This would include any gynaecological procedure or test which is planned or has taken place, and its corresponding course and outcome.

9.3.5 Medicinal Product

This is an observational study of real-world treatment practices and outcomes. Patients will be invited to enrol in the study only after the decision to initiate treatment with Esmya has been made by the investigator and the patient (not applicable to the subjects previously treated with UPA 5 or 10 mg during the long term Phase III trials). No study medication will be provided as part of the study. The investigator will make all treatment decisions according to his/her standard medical practice and will provide prescriptions for his/her patients, as appropriate.

At each visit the investigator will report the treatment received, where applicable, since the last visit. This will include start and stop dates of Esmya, dose and frequency of Esmya, and any change in regimen during a course.

9.4 Data Sources

All data for the variables/outcomes are collected at each patient visit and entered into web-based Electronic Data Capture (EDC) forms, by the site staff, and originate from the clinical records used by each site according to standard local practice and data collection standards.

9.5 Study Size

The objectives of the study are to evaluate the long term safety of Esmya, in particular the endometrial safety, and the current prescription and management patterns of Esmya in a long term treatment setting. Given the descriptive nature of the study, the target sample size is not based on any formal test of hypotheses. A sample of 1,500 patients is felt to be a strong basis to assess safety and treatment patterns, and will provide sufficient data to perform analyses for outcomes related to treatment with Esmya.

9.6 Data management

All investigator-reported data and the EQ-5D data will be entered via a secure web-based Electronic Data Capture (EDC) study database. Site personnel will be provided with secure usernames and passwords in order to enter study data into the EDC system. All sites will be fully trained in using the EDC system, including the electronic Case Report Form (eCRF) completion guidelines. It is the Investigator or designee's responsibility to ensure the accuracy of the data entered in the eCRFs.

The data management group will be responsible for data processing, in accordance with agreed data management procedures. Analyses will be performed using Statistical Analysis System (SAS) (Version 9.3 or later) for Windows software or higher.

9.7 Data Analysis

9.7.1 Statistical Analysis

The majority of statistical analyses will be descriptive, reporting patient counts, means, standard deviations, medians, minima, and maxima for continuous variables (e.g., age and duration of symptomatic uterine fibroids) and frequencies and percentages for categorical variables (e.g., disease symptoms, prescription pattern, diagnostic test results). Two-sided 95% confidence intervals will be estimated as appropriate and reported along with p-values to facilitate the interpretation of the significance of the findings. These findings will be compared to published epidemiological data on pre-menopausal women with abnormal uterine bleeding (AUB), where available.

Baseline data (i.e. data collected prior to the first administration of Esmya), including relevant demographic characteristics will be summarised for all treated subjects.

Full details of all analysis to be carried out will be presented in the Statistical Analysis Plan (SAP).

9.7.2 Analysis sets

All subjects who receive at least one dose of medicinal product (Esmya), or who were previously exposed to UPA 5 or 10 mg in long term Phase III clinical trials PGL09-027 (PEARL III extension; including patients of PGL11-024 (PEARL extension 2)), or PGL11-006 (PEARL IV) will be included in the main analysis population (i.e. Safety / Intention to Treat (ITT)).

9.7.3 Method of Handling missing data

No data will be imputed, only reported values will be used for the purpose of the analysis.

9.7.4 Sub-group Analyses

In addition to the main analysis population, sub-group analyses will be carried out on:

- All patients who completed at least 4 courses within the study period (60 months)
- All patients who had any individual treatment course with a duration > 3 months (i.e. continuous use)
- All patients who were previously treated in the Long Term Phase III studies.

9.8 Quality Control

The database will be managed by the CRO on a physically and logically secure computer server in accordance with written security policies. The EDC system meets approved established standards for the security of health information and is validated. The system also meets the International Committee on Harmonisation (ICH) guideline E6R1 regarding electronic study data handling and is available for audit upon request. Patient confidentiality will be strictly maintained.

The CRO maintains high data quality standards and utilizes processes and procedures to repeatedly ensure that the data are as clean and as accurate as possible when presented for analysis. Data quality is enhanced through a series of programmed data quality checks that automatically detect and prevent the entry of out-of-range or anomalous data. A remote data quality audit may be performed at various times throughout the study on collected data

All investigator completed forms, original informed consent forms and Patient Reported Outcome (PRO) forms will be maintained at the study site for a period of 2 years after study completion.

The Investigator is to ensure that the eCRFs are completed in a timely manner and to allow a Sponsor representative (Clinical Research Associate (CRA) periodic access to eCRFs, patient records and all study-related materials. The frequency of monitoring visits will be determined by factors such as the design of the study, the frequency of patient visits and the site enrolment rate. In order to verify that the study is conducted in accordance with applicable laws, regulatory requirements and the study protocol, and that the data are authentic, accurate and complete, the study monitor will review study documents and conduct source data verification on selected patient charts. The CRA is able to access the eCRFs remotely during

the course of study. Upon study completion, the Sponsor CRA or monitor will conduct a Study Termination visit. This will involve collection of any outstanding documentation.

9.9 Limitations of the research methods

This is a non-interventional study, to assess real life use of Esmya, and therefore the assessments (including biopsies) will be according to standard medical practice, and not dictated at specific timepoints. This may result in some inter-patient differences and lack of information to detect or assess properly the identified or potential safety risks or missing information as specified in this protocol.

9.10 Other aspects

N/A

10 PROTECTION OF HUMAN SUBJECTS

All patients enrolled into the study will be treated according to the national and EU requirements to ensure their well-being and rights. They will also be treated according to the guidelines for non-interventional post-authorisation safety studies.

11 MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

The following safety information will be collected throughout the course of the study:

- all gynaecological Adverse Events considered as related or not related to Esmya,
- Serious Adverse Events (SAEs) considered as related or not related to Esmya,
- non-serious Adverse Drug Reactions (ADRs),
- Adverse Events (AEs) leading to Esmya treatment discontinuation (treatment discontinuation defined as stopping treatment with Esmya during a treatment course)
- all pregnancies occurring from treatment start until the end of the study
- all liver related Adverse Events considered as related or not-related to Esmya

Once the investigator becomes aware of a non-serious ADR or an AE leading to Esmya treatment discontinuation, the information should be reported on an AE report form in the study EDC system. Once the investigator becomes aware of an SAE, the information should be recorded on an AE Report Form in the study EDC system and in a paper SAE form and sent to sponsor no later than within 24 hours of the site becoming aware of the event. SAE reports should be printed, signed by the investigator and sent by email / fax to Gedeon Richter Romania Esmya case processing centre (GRRO) for processing and safety regulatory reporting, as appropriate.

E-mail: esmya_safety@gedeon-richer.ro

Fax: **00 40-265 201 316**

Phone: **00 40-265 257 011 (dedicated to Medical Information)**

GRRO safety team will obtain as much information as possible regarding the AE/SAE using standard data collection tools. The investigator will be asked to provide an assessment of whether the AE/SAE is related to Esmya/UPA treatment, or is related to other treatments or procedures, or other medical history, or to any other cause.

All pregnancies occurring from treatment start until the end of the study must be recorded using the Pregnancy Surveillance Form and reported within 7 working days from notification to the contact details above. The outcome of pregnancies should be followed with investigator by GRRO safety team.

Intensity and severity

The severity of AEs must be assessed by investigators according to the following definitions.

Mild:	The subject is aware of the event or symptom, but the event or symptom is easily tolerated (e.g. no reduction in daily activities is required).
Moderate:	The subject experiences sufficient discomfort to interfere with or reduces her usual level of activity.
Severe:	Significant impairment of functioning: the subject is unable to carry out usual activities and/or the subject's life is at risk from the event.

Causality Assessment

The causality assessment of an AE to the Esmya will be rated as follows by the investigator:

Not related:	A causal relationship is unlikely or can be definitely excluded and another documented cause of the AE (other drugs, therapeutic interventions or underlying conditions) is most plausible.
Related:	A causal relationship is clinically/biologically plausible or highly plausible, and there is a plausible time correlation between the onset of the AE and administration of the Esmya. This means that there are facts (evidence) or arguments to suggest a causal relationship.

Adverse Event (AE)

An adverse event (AE) is any untoward medical occurrence in a subject in the study. It does not necessarily have a causal relationship with the treatment. An AE can, therefore, be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease occurring after first exposure to Esmya, whether or not considered related to the product.

Adverse Drug Reaction (ADR)

All noxious and unintended responses to a medical product related to any dose administered should be considered as adverse drug reactions. A reaction, in contrast to an event, is characterised by the fact that a causal relationship between the drug and the occurrence is at least a reasonable possibility.

Serious Adverse Event (SAE)

A serious adverse event/adverse drug reaction is any untoward medical occurrence that at any dose:

results in death,

i.e., the AE causes or contributes to the death.

is life-threatening,

i.e., the AE places the subject at immediate risk of death; it does not refer to an AE which hypothetically might have caused death, if it were more severe.

requires in-patient hospitalisation or prolongation of existing hospitalisation,

i.e., the AE requires at least an overnight admission or prolongs a hospitalisation beyond the expected length of stay. Hospital admissions for surgery planned before study entry, for social reasons, for any elective surgery (e.g., plastic surgery) or for normal disease management (including treatment adjustment) are NOT to be considered as SAE according to this criterion (i.e., if the protocol or the standard management of the disease under study requires planned hospitalisation e.g. myomectomy).

results in persistent or significant disability / incapacity,

i.e., the AE resulted in a substantial disruption of the subject's ability to conduct normal activities.

is a congenital anomaly / birth defect,

i.e., an adverse event outcome in a child or foetus of a subject exposed to the marketed medicinal product before conception or during pregnancy.

is an important medical event, i.e., is medically significant.

Medical and scientific judgment should be exercised in deciding whether an adverse event/reaction is serious. Important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above should also be considered serious. Examples of such events are intensive treatment in an emergency room, or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation or development of drug dependency or drug abuse.

All AE's reported during the study will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Exact procedures for handling all reported AEs will be described in the Safety Management Plan (SMP) for the study.

12 PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

As stated, progress reports will be carried out on a yearly basis from date of First Patient In (FPI) (i.e. first patient meeting the exclusion/inclusion criteria enrolled in the study) to report progress of the study and results on major endpoints, where appropriate. A final Report will be generated at the end of the Study. It is planned that these progress reports may be used as the basis of abstracts, presentations during scientific symposiums, company stand-alone meetings or for the production of publications, where it is felt appropriate. These forms of communication/dissemination will be used where it is felt the data could provide new or updated safety data to the scientific community on the use of Esmya for patients undergoing long term treatment for uterine fibroids.

13 REFERENCES

1. Wallach EE and Vlahos NF. Uterine myomas: an overview of development, clinical features, and management. Obstet Gynaecol 2004;104:393–406.

2. Donnez J and Jadoul P. What are the implications of myomas on fertility? A need for a debate? Hum Reprod 2002;17:1424–30.

3. Stewart EA. Uterine fibroids and evidence-based medicine. Not an oxymoron. N Engl J Med 2012;366:471-3

4. Donnez J, Schrurs B, Gillerot S, Sandow J, Clerckx F. Treatment of uterine fibroids with implants of gonadotropin-releasing hormone agonist: assessment by hysterography. Fertil Steril 1989;51:947–50.

5. Lethaby A, Vollenhoven B, Sowter M. Pre-operative GnRH analogue therapy before hysterectomy or myomectomy for uterine fibroids. Cochrane Database Syst Rev 2001;(2):CD000547.

6. Zapata LB, Whiteman MK, Tepper NK, Jamieson DJ, Marchbanks PA, Curtis KM. Intrauterine device use among women with uterine fibroids: a systematic review. Contraception 2010;82:41–55.

7. Melis GB, Piras B, Marotto MF et al. Pharmacokinetic evaluation of ulipristal acetate for uterine leiomyoma treatment. Expert Opin Drug Metab Toxicol 2012;8(7):901-8.

8. Gainer EE and Ulmann A. Pharmacologic properties of CDB(VA)-2914. Steroids 2003;68:1005–11.

9. Horak P, Mara M, Dundr P et al. Effect of a selective progesterone receptor modulator on induction of apoptosis in uterine fibroids in vivo. Int J Endocrinol 2012;2012:436174 .

10. Pohl O, Osterloh I, Gotteland JP. Ulipristal acetate - safety and pharmacokinetics following multiple doses of 10-50 mg per day. J Clin Pharm Ther 2013 Apr 3

11. Chabbert-Buffet N, Meduri G, Bouchard P, Spitz I. Selective progesterone receptor modulators and progesterone antagonists: mechanisms of action and clinical applications. Human Reproduction Update, Vol. 11, No.3 pp 293-307, 2005

12. Spitz I. Clinical Utility of progesterone receptor modulators and their effect on the endometrium. Curr Opin Obstet Gynaecol 21: 318-324, 2009

13. Donnez J, Tatarchuk TF, Bouchard P et al. Ulipristal acetate versus placebo for fibroid treatment before surgery. N Engl J Med 2012;366(5):409-20.

14. Donnez J, Tomaszewski J, Vazquez F et al. Ulipristal acetate versus leuprolide acetate for uterine fibroids. N Engl J Med 2012;366(5):421-32.

15. Mutter GL, Bergeron C, Deligdisch L, Ferenczy A, Glant M, Merino M, et al. The spectrum of endometrial pathology induced by progesterone receptor modulators. Mod Pathol 2008;21:591–8.

16. Fiscella J, Bonfiglio T, Winters P, Eisinger SH, Fiscella K. Distinguishing features of endometrial pathology after exposure to the progesterone receptor modulator mifepristone. Hum Pathol 2011;42:947–53.

17. Ioffe OB, Zaino RJ, Mutter GL. Endometrial changes from short-term therapy with CDB-4124, a selective progesterone receptor modulator. Mod Pathol 2009;22:450–9.

18. Williams AR, Bergeron C, Barlow DH, Ferenczy A. Endometrial morphology after treatment of uterine fibroids with the selective progesterone receptor modulator, ulipristal acetate. Int J Gynaecol Pathol 2012;31:556–69.

19. Donnez J, Vazquez F, Tomaszewski J et al. Long-term treatment of uterine fibroids with Ulipristal acetate. http://dx.doi.org/10.1016/j.fertnstert.2014.02.008

20. Donnez J et al. Efficacy and safety of repeated use of UPA in uterine fibroids. Fertility & Sterility 2014; Vol 103, No. 2, 519-526.

Annexes

13.1 Annex 1: List of Stand Alone Documents

Number	Document Reference Number	Date	Title
1	PGL14-001-Annex 1-1	List to be confirmed	Contact Details and List of All Investigators (available on request)

13.2 Annex 2: ENCePP Checklist for Study Protocols

See separate Annex

13.3 Annex 3: Additional Information

13.4 Sample of the EQ-5D quality of life questionnaire

Health Questionnaire

English version for the UK
(validated for Ireland)

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about ❑

I have some problems in walking about ❑

I am confined to bed ❑

Self-Care

I have no problems with self-care ❑

I have some problems washing or dressing myself ❑

I am unable to wash or dress myself ❑

Usual Activities *(e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities ❑

I have some problems with performing my usual activities ❑

I am unable to perform my usual activities ❑

Pain/Discomfort

I have no pain or discomfort ❑

I have moderate pain or discomfort ❑

I have extreme pain or discomfort ❑

Anxiety/Depression

I am not anxious or depressed ❑

I am moderately anxious or depressed ❑

I am extremely anxious or depressed ❑

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today