The UCON Trial:

Ulipristal acetate versus conventional management of heavy menstrual bleeding (HMB; including uterine fibroids): a randomised controlled trial and exploration of mechanism of action

PROTOCOL

UCON Trial Management Committee

Chief Investigator

Professor Hilary Critchley
University of Edinburgh
MRC Centre for Reproductive Health
The Queen's Medical Research Institute
47 Little France Crescent
Edinburgh EH16 4TJ
Tel: 0131 242 6858
Email hilary.critchley@ed.ac.uk

Trial Coordination and Statistics

Dr Jane Daniels
University of Birmingham
Email: j.p.daniels@bham.ac.uk

Mr Lee Priest
University of Birmingham
Email: l.priest.1@bham.ac.uk

Mr Lee Middleton
University of Birmingham
Email: l.j.middleton@bham.ac.uk

Mr Konstantinos Tryposkiadis
University of Birmingham
Email: k.tryposkiadis@bham.ac.uk

Clinical Lead Investigators

Professor Justin Clark
Birmingham Women's Hospital
Tel: 0121 472 1377 Ext 4219
Email: Justin.Clark@bwhct.nhs.uk

Professor Mary Ann Lumsden
University of Glasgow
Tel: 0141 201 8616
Email: maryann.lumsden@glasgow.ac.uk

Dr Dharani Hapangama
University of Liverpool
Tel: 0151 795 9559
Email: dharani.hapangama@liverpool.ac.uk

Dr Lucky Saraswat
University of Aberdeen
Tel: 01224 438 419
Email: lucky.saraswat@nhs.net

Research Fellow (Clinical Co-Investigator)

Dr Paul Smith
Birmingham Women's Hospital
Tel: 07932 044 361
Email: paul.smith@doctors.org.uk

Lead Pathologist

Professor Alistair Williams
University of Edinburgh
Tel: 0131 242 7120
Email: a.williams@ed.ac.uk

Scientific Leads for Mechanistic Studies

Professor Hilary Critchley
University of Edinburgh
Tel: 0131 242 6858
Email: hilary.critchley@ed.ac.uk

Dr Scott Semple
University of Edinburgh
Tel: 0131 242 7757
Email: scott.semple@ed.ac.uk

Professor Neil Roberts
University of Edinburgh
Tel: 0131 242 7769
Email: neil.roberts@ed.ac.uk

Kiaming Yin
University of Edinburgh
Tel: 0131 242 9124
s1158296@sms.ed.ac.uk

Research Collaborators

Dr Michael Thrippleton
University of Edinburgh
Tel:
Email: m.j.thrippleton@ed.ac.uk

Professor Philippa Saunders
University of Edinburgh
Tel: 0131 242 6388
Email: p.saunders@ed.ac.uk

Dr Pamela Warner
University of Edinburgh
Tel: 0131 650 3248
Email: p.warner@ed.ac.uk

Trial Management Group

Professor Hilary Critchley, University of Edinburgh

Professor Alistair Williams, University of Edinburgh

Professor Neil Roberts, University of Edinburgh

Dr Jane Daniels, University of Birmingham

Mr Lee Priest, University of Birmingham

Mr Lee Middleton, University of Birmingham

Mr Konstantinos Tryposkiadis, University of Birmingham

Trial Steering Committee (TSC)

Professor Hilary Critchley, University of Edinburgh

Dr Jane Daniels, University of Birmingham

Mr Lee Priest, University of Birmingham

Sponsor Representative, University of Edinburgh

Trial Steering Committee (TSC) Independent Members

Mr Jim Thornton (Chair), Nottingham City Hospital

Dr Christian Becker, University of Oxford

Dr Emma Crosbie, University of Manchester

Professor Lesley Regan, Imperial College London

Dr Ying Cheong, University of Southampton

Ms Emily O'Toole, PPI Representative

Data Monitoring and Ethics Committee (DMEC)

For interim analyses and response to specific concerns

Professor Richard Gray (Chair), Clinical Trial Service Unit and Epidemiological Studies Unit (CTSU), Oxford

Professor Glenn McCluggage, Queen's University of Belfast

Ms Lelia Duley, Nottingham Clinical Trials Unit, Nottingham

UCON Trials Office

Birmingham Clinical Trials Unit (BCTU)
Institute of Applied Health Research
Public Health Building
University of Birmingham
Edgbaston
Birmingham
B15 2TT

Telephone: 0121 414 6665

E-mail: lothian.ucon@nhs.net

Website: www.birmingham.ac.uk/ucon

Trial Coordination

Mr Lee Priest — Email: l.priest.1@bham.ac.uk, l.priest@nhs.net

Statistics

Mr Lee Middleton — Email: l.j.middleton@bham.ac.uk

Mr Konstantinos Tryposkiadis — Email: k.tryposkiadis@bham.ac.uk

Database Development

Mr Adrian Wilcockson — Email: a.c.wilcockson@bham.ac.uk

Clinical queries should be directed during office hours to the Chief Investigator. Other queries should be directed to the UCON Trials Office.

FOR RANDOMISATIONS

Telephone:	0800 953 0274 (UK)
Website	https://www.trials.bham.ac.uk/UCON

Version Number

Protocol Version 3.0 – 25th January 2016

Protocol Versions

Version No – Date/ Amendment Type	Summary of Changes Made
3.0 – 25th January 2016/ Substantial Amendment (AM3)	MRC logo added, list of abbreviations updated, change of BCTU staff. Trial Summary updated ('at least 5 NHS hospitals') '1.1 Background' – reference to Mirena removed. '2.2.2 Secondary Outcomes' updated. '4.2.1 Inclusion criteria' – bleeding 'at intervals of 21 – 42 days removed'. '5.1.3 Gynaecology Clinic Patient Identification' – figure 1 updated to clarify that blood samples are to observe serum haemoglobin and oestradiol levels; '5.5.5 Withdrawal of Study Participants' – clarification of duration LNG-IUS may be used depending on manufacturer. '6.1.3 Levonorgestrel (Reference)' – clarification that in context of trial, of LNG-IUS may be manufactured by two companies. '6.1.5 Marketing Authorisation Holder' – marketing authorisation codes for Levosert added. '6.3 Dose Changes' – acceptable timeframe for women participant start taking UPA. '6.4.2 Monitoring Compliance' – Clarification of drug compliance. '7.2 Timing of Study Assessments' clarification of menstrual blood loss diary completion. '7.3 Outcomes Collected at Study Assessments' – clarification that 12 month MRI taken at Edinburgh will be performed in final week of treatment. '8.1.1 Participant Questionnaire' – EuroQol/ ICECAP added. '8.1.3 Clinical Assessment and Randomisation Form' – clarification of serum blood levels observed. '9.2.4 Handling missing data and other sensitivity analysis – clarification of follow-up.
2.0 – 30th June 2015/ Substantial Amendment (AM2)	Admin changes - trial logo added, TSC/ UCON Trials Office Updated, trial registration numbers updated. Trial Summary – eligibility updated. '2.2 - RCT Outcomes' section updated with surgical intervention. '3.1 Design' clarified. '4.1 number of participants' clarified. '4.2 – Eligibility' clarified. '5 Participant Selection and enrolment'. Figure 1 updated. '5.2 Consenting for Screening for Eligibility' clarified. '5.5 Randomisation' clarified. Figure summarising patient pathway for Edinburgh patients inserted. '6 – Investigational Medicinal Products' clarified. '7 Study Assessments Overview' clarified. '8 – Data Collection' clarified. '9 – Statistics and Data Analysis'. '10 – Adverse Events and Pharmacovigilance'. '11 - Trial Management and Oversight Arrangements' admin changes.

Trial Registration Numbers

Sponsor	University of Edinburgh and NHS Lothian
Sponsor Reference Number	UCON
Funder	Medical Research Council (MRC) and National Institute for Health Research (NIHR) - Efficacy and Mechanism Evaluation (EME)
Funding Reference Number	12/206/52
Chief Investigator	Professor Hilary Critchley
Sponsor Representative	Dr Vikki Young
EudraCT Number	2014-003408-65
REC Number	14/LO/1602
MHRA CTA Reference Number	275860016
ISRCTN Number	20426843
UKCRN Portfolio ID	18534
University of Birmingham Ref	ERN_14-0938
IRAS Project ID	145282
NHS Research Scotland (NRS) Number	15-GY30

PROTOCOL APPROVAL SIGNATURES

The investigators and the sponsor have discussed this protocol. The investigators agree to perform the investigation and to abide by this protocol except in case of medical emergency or where departures from it are mutually agreed in writing.

This protocol was written in accordance with the sponsor's procedures available at:
http://www.accord.ed.ac.uk/standardopprocs/CRSOPs.html

Chief Investigator

Professor Hilary Critchley		12th April 2016
University of Edinburgh	Signature	Date

Trial Statistician

Mr Lee Middleton		12th April 2016
University of Birmingham	Signature	Date

Sponsor Representative

Dr Fiach O'Mahony		08 April 2016
University of Edinburgh	Signature	Date

LIST OF ABBREVIATIONS

ACCORD	Academic and Clinical Central Office for Research & Development - Joint office for University of Edinburgh and NHS Lothian
AE	Adverse Event
AR	Adverse Reaction
BCTU	Birmingham Clinical Trials Unit
CI	Chief Investigator
CRF	Case Report Form
DMEC	Data Monitoring and Ethics Committee
EudraCT	European Clinical Trials Database
EQ-5D-5L	EuroQol-5 Dimension-5 Level (Quality of Life Questionnaire)
GCP	Good Clinical Practice
ICECAP-A	ICEpop CAPability measure for Adults (Quality of Life Questionnaire)
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trial Number
LNG-IUS	Levonorgestrel releasing intra-uterine system
MHRA	Medicines and Healthcare Products Regularity Authority
MRI	Magnetic Resonance Imaging
NIHR	National Institute for Health Research
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMG	Trial Management Group
TMF	Trial Master File
TSC	Trial Steering Committee
UAR	Unexpected Adverse Reaction
UPA	Ulipristal Acetate
UFS-QoL	Uterine Fibroid Symptom-Quality of Life

CONTENTS

TRIAL SUMMARY

DESIGN:	A multicentre, randomised controlled trial with an embedded mechanistic evaluation of UPA compared to LNG-IUS.
SETTING:	At least 5 NHS hospitals within the United Kingdom
TARGET POPULATION:	Women aged over 18 years or over, who are presenting to primary and/or secondary care with HMB. Exclusion criteria: Post-menopausal, a uterus >14 week fibroid uterus and/or cavity length >11cm, submucosal fibroids >2cm in diameter, contraindications to UPA or LNG-IUS; intention to continue current use of CYP3A4 inhibitors (e.g. erythromycin propionate; ketoconazole); intention to continue current use of CYP3A4 inducers (Phenytoin, carbamazepine, rifampicin, St John's Wort), intention to continue current use of P-glycoprotein substrate (e.g. digoxin); past, current or suspected diagnosis of endometrial hyperplasia or neoplasia, severe hepatic impairment; Epilepsy managed with carbamazepine, phenytoin; significant renal impairment; pregnant; current plans to become pregnant within 12 months; currently breastfeeding, severe asthma that is not sufficiently controlled by oral glucocorticoids; past or current known history of uterine, cervical, ovarian or breast cancer; receiving P-glycoprotein substrates; current use progestagen-releasing intrauterine device (except if allocated within UCON), intention to continue continued regular use of Mefenamic acid, intention to continue intention to continue regular use of Mefenamic acid, intention to continue regular use of GnRH analogues, continued regular use of Progestagen-only contraceptive, intention to continue continued regular use of combined oral contraceptive pills, intention to continue hormonal replacement therapy.

HEALTH TECHNOLOGIES ASSESSED:	Those allocated to UPA will receive proprietary ulipristal acetate 5mg, orally, once daily. The participant should start taking UPA within the first five days of starting menstrual bleeding. Women will be instructed to take UPA in 3 courses according to the following cyclical regime (± 5 days): 1. One 5mg tablet of UPA to be taken daily for 12 weeks then stopped for 4 weeks, when light vaginal bleeding may occur (withdrawal bleed). 2. After 4 weeks off treatment, regardless of whether they experience a withdrawal bleed, they should recommence UPA 5mg daily for another 12 weeks, then stop for 4 weeks, when they will expect to have a withdrawal bleed. 3. Repeat as for treatment course (2). OR Levonorgestrel-releasing intra-uterine system, retained for up to 5 years (depending on the product and manufacturer). Where contraception is required, the woman will be asked to use a barrier method.

OUTCOME MEASURES:	Primary Outcome: The primary outcome measure is the condition-specific Menorrhagia Multi-Attribute Scale (MMAS) designed and validated to capture the impact of HMB on women's day-to-day life (1). HMB is a subjective problem and quality of life is affected by practical difficulties and the impact on social life, psychological wellbeing, physical health, work routine and family life. The menorrhagia multi-attribute utility assessment (MMAS) questionnaire attempts to capture the consequences of HMB on these domains with 6 questions each with 4 levels of response. Summary scores range from 0 (not affected) to 100 (worst affected). The primary time point for analysis will be at 12 months. Secondary Outcome measures: • Menstrual bleeding will be captured by validated Pictorial Blood Loss Assessment Chart (PBAC) (14). The standard PBAC is a validated and well used assessment of menstrual blood loss in women. The PBAC will be supplemented by visual analogue scales for menstruation duration, regularity and pelvic pain. • Uterine Fibroid Symptom and Quality of Life (UFS-QoL) instrument, which contains a health related quality of life (HRQoL) domain and a symptom domain (15). This instrument will be only given to women diagnosed with fibroids. • Sexual Activity Questionnaire (16), a measure of sexual functioning, used in other HMB trials. The sexual activity questionnaire is a valid, reliable and acceptable measure for describing the sexual functioning of women in terms of pleasure and discomfort. It is quick and easy to administer and has good face validity delineating between the sexual functioning of pre and post-menopausal women. • Satisfaction with treatment outcome measured on a 5-point Likert scale. Specific statements about the experience and the acceptability of the treatment and the beliefs about the value of the treatment will be elicited from the participants. • Surgical intervention (hysterectomy or endometrial ablation) • Adherence to trial treatments, as reported by the participant. • Serious adverse events and reactions reported by participants, principally those that are serious and detailed in the respective Summary of Product Characteristics (SmPC) and those that are unexpected. • Clinical measurements to assess safety and efficacy will include pelvic ultrasound (endometrial appearance; fibroid volume, presence of fibroids) and endometrial biopsies (reported according to pre-agreed criteria by independent pathologists blinded to treatment allocations). Blood samples will be taken to observe serum haemoglobin and oestradiol levels. **Functional and mechanistic outcomes** • Impact on endometrial tissue architecture including regulation of the vascular compartment • Impact on endometrial steroid responsiveness, proliferation

	Functional and mechanistic outcomes • Impact on endometrial tissue architecture including regulation of the vascular compartment • Impact on endometrial steroid responsiveness, proliferation, cell survival and inflammatory processes • Expression of genes implicated in pre-malignant change including tumour suppressors • Effects on uterine/ fibroid structure and vascularity as determined by MRI-DCE and high resolution structural MRI
ANALYSIS:	Analysis of the primary outcome will be performed using a linear regression model to estimate differences in MMAS responses between groups at each time-point, including baseline score and the minimisation variables as covariates. Twelve months will be considered the primary outcome time. Point estimates, 95% confidence intervals and p-values from two-sided tests will be calculated for all main outcome measures. The mechanistic sub-study will investigate possible changes in defined histological, immunological and molecular/ cellular parameters within treatment groups over time and will be analysed using paired t-tests following an appropriate transformation and also by using non-parametric methods (Wilcoxon signed rank test) for confirmation.
SAMPLE SIZE:	The trial has been designed to detect a 13 points difference in MMAS score between the two groups at 12 months. To detect this size of difference (approximately 0.5 standard deviations) with 90% power (p=0.05) will require 86 women per group, 172 in total. To allow for a 20% loss to follow-up or pregnancy, the sample size has been inflated to 220 women in total. In the mechanistic evaluation (performed at the Royal Infirmary of Edinburgh only), a sample size of 20 would give >90% power (p=0.05) to detect a change from baseline – for example in PH3 immunoscore in the endometrium of >1 standard deviation.

1 INTRODUCTION

1.1 BACKGROUND

Menstrual bleeding complaints affect quality of life and comprise a substantial societal burden, including major impact on health care use and costs. In the UK, 1 million women annually seek help for heavy menstrual bleeding (HMB; Clinical Guideline 44; http://www.nice.org.uk/guidance/cg44) and reported treatment costs exceed £65m; an estimated 3.5 million work-days are lost annually (1).

Current commonly prescribed medical treatments for HMB include COX-inhibitors, anti-fibrinolytic therapy, and the levonorgestrel-releasing intra-uterine system (LNG-IUS). NICE recommends LNG-IUS as the first line medical treatment. The LNG-IUS significantly reduces the burden of heavy menstrual bleed compared to non-hormonal treatments, substantially reduces menstrual blood loss, often resulting in amenorrhoea, but the unpredictable unscheduled bleeding may be problematic, with up to a third ceasing use within 2 years (2, 3).

An exciting new group of pharmacological agents, called selective progesterone receptor modulators (SPRMs) are in development and have the potential to provide effective oral treatment for HMB. These SPRMs impart a tissue-specific partial progesterone antagonist effect, acting on progesterone receptors in both endometrial and underlying myometrial tissue. Ulipristal Acetate (UPA) is the only SPRM to have been licensed for use in clinical practice albeit restricted to two cycles of 3 month pre-treatment of fibroids prior to surgical removal. The introduction of this drug followed evaluation in two concurrent randomised controlled trials (RCTs) (4); 'PEARL I' assessed the efficacy of UPA 5mg and 10 mg daily on uterine bleeding and fibroid volume against placebo and 'PEARL II' assessed the efficacy and side effects of UPA versus the gonadotrophin-releasing hormone analogue (GnRHa) leuprolide acetate for treating symptomatic uterine fibroids prior to surgery (4). Both trials demonstrated control of HMB in over 90% of women and amenorrhoea in over 70% women. Control of HMB was achieved significantly more quickly in the UPA group. There was a statistically significant reduction in uterine fibroid size (-21% in the 5mg and -12% in the 10mg groups). Compliance with treatment over 3 months was high in both studies (96% and 98%) and reported side-effects were limited to minor complaints, of which headache (4%) and breast complaints (4%) were the most common, with no difference between active drug and placebo.

Different classes of SPRM induce distinct endometrial morphology, which can be confused with complex hyperplasia. To date detailed analysis of endometrial histology has been limited to treatment with UPA for 3 months (5, 6); detailed histological evaluation showed altered architectural glandular features including extensive cystic dilatation. The glandular epithelium appeared inactive or contained abortive subnuclear vacuolization, occasional mitoses, and apoptosis. Histology returned to normal after discontinuation of treatment (6). Treatment of monkeys for 39 weeks revealed similar endometrial histology to that in women (7).

PTEN is a tumour suppressor gene product, described as a gatekeeper for initiation of carcinogenesis in the endometrium (8, 9). Loss of PTEN function occurs as an early event in endometrial carcinogenesis and has been proposed as a biomarker for premalignant disease even in histologically normal endometrium (8, 10). Progesterone plays an important role in eliminating PTEN-deficient endometrial cells when administered via a progestin-releasing intrauterine device (11) or systemically (12). A compound with progesterone antagonist activity, such as UPA, may raise concerns of an unfavourable effect on PTEN expression and thus on the potential to influence predisposition to latent endometrial precancerous lesions. Hence study of PTEN in women administered UPA is important.

1.2 RISKS AND BENEFITS

Whilst short term use of UPA has been shown to be effective in treating HMB associated with uterine fibroids (3-10cm in size), UPA has the potential to provide a safe, fertility preserving, rapidly effective and convenient oral medical treatment, suitable for women with HMB throughout reproductive age whether associated with fibroids or not. However, whilst UPA has the potential to revolutionise the treatment of HMB, our understanding of the mechanism and location of action of UPA is unclear, as is its longer term safety and effectiveness. As with earlier SPRMs, UPA induces non-physiological endometrial changes known as progesterone-receptor modulator-associated endometrial changes (PAECs) in 62% of participants receiving 5mg UPA, although there is no evidence these are premalignant. Whilst these changes are reported to be reversed in all women after 6 months of ceasing treatment, the mechanisms underlying these changes and their clinical significance remain uncertain. More recent unpublished data provide further reassurance of the reversibility of PAEC - if endometrial biopsy is performed after one normal menstrual shedding after treatment withdrawal, the incidence of PAEC is reduced to around 30%, a rate that remains similar after up to 4 UPA treatment cycles (Personal communication A Williams).

1.3 RATIONALE FOR STUDY

The rationale for using UPA to control HMB is because HMB is a clinical area of unmet need, with a community prevalence of 25%, and can significantly impact on women's lives and burden individuals and healthcare systems. HMB often co-exists with uterine fibroids, benign tumours of uterine muscle present in up to 80% of women of reproductive age. Medical therapy for HMB, particularly when fibroids are present, may be either ineffective or associated with unacceptable side effects. Preservation of fertility is an issue for many women, given the trend for later births.

It is clear that there is an urgent need to develop safe, simple, acceptable, fertility-sparing medical treatments for HMB. SPRMs may provide a solution in light of the mounting evidence that progesterone and the progesterone receptor play a pivotal role in both menstruation and fibroid growth and development. The PEARL studies demonstrated control of HMB in over 90% of women and amenorrhoea in over 70% women. There were no serious side effects or complications associated with UPA; adverse events were limited to minor complaints. However despite profound therapeutic potential, robust data on long term effectiveness and the mechanisms of action of SPRMs in women with HMB remain to be elucidated. There is an urgent need to evaluate the use of UPA against current best medical treatment for all women with HMB.

2 STUDY OBJECTIVES

2.1 RCT OBJECTIVES

2.1.1 Primary Objective

- Determine if UPA is more effective at reducing the burden of HMB symptoms than LNG-IUS after 12 months of treatment.

2.1.2 Secondary Objectives

- Ascertain whether UPA use beyond 3 months and up to 12 months duration is associated with histological changes to the endometrium, and if so, whether this compromises safety.

- Ascertain whether UPA is more effective than LNG-IUS in relation to menstrual blood loss, sexual activity, generic quality of life, satisfaction with treatment, patient reported adverse events, and compliance at 3, 6 and 12 months.
- Determine the response to UPA and LNG-IUS treatment difference in the presence of uterine fibroids in terms of (i) alleviation of HMB and (ii) change in uterine/fibroid volume.

2.1.3 Mechanistic Sub-study Objectives

To understand how UPA causes a reduction in menstrual bleeding and uterine/ fibroid volume in women with HMB, we will determine whether:

- Administration of UPA alters endometrial cell function (proliferation, apoptosis, expression of steroid receptors, tumour suppressors or inflammatory mediators).
- UPA reduces blood flow and blood volume in the endometrium, junctional zone, outer myometrium and fibroid tissue.
- UPA alters the volume fraction of the extracellular matrix in the above tissues.
- UPA reduces uterine and fibroid volume.

2.2 RCT OUTCOMES

2.2.1 Primary outcome

The primary outcome measure is the condition-specific Menorrhagia Multi-Attribute Scale (MMAS) designed and validated to capture the impact of HMB on women's day-to-day life (13). HMB is a subjective problem and quality of life is affected by practical difficulties and the impact on social life, psychological wellbeing, physical health, work routine and family life. The menorrhagia multi-attribute utility assessment (MMAS) questionnaire attempts to capture the consequences of HMB on these domains with 6 questions each with 4 levels of response. Summary scores range from 0 (not affected) to 100 (worst affected). The primary time point for analysis will be at 12 months.

2.2.2 Secondary outcomes

- Menstrual bleeding will be captured by validated Pictorial Blood Loss Assessment Chart (PBAC) (14). The standard PBAC is a validated and well used assessment of menstrual blood loss in women. The PBAC will be supplemented by visual analogue scales for menstruation duration, regularity and pelvic pain.
- Uterine Fibroid Symptom and Quality of Life (UFS-QoL) instrument, which contains a health related quality of life (HRQoL) domain and a symptom domain (15).
- General quality of life questionnaires - EuroQoL-5D *(EQ-5D-5L) ((16)) and ICECAP-A ((17)).*
- Sexual Activity Questionnaire (18), a measure of sexual functioning, used in other HMB trials (3). The sexual activity questionnaire is a valid, reliable and acceptable measure for describing the sexual functioning of women in terms of pleasure and discomfort. It is quick and easy to administer and has good face validity delineating between the sexual functioning of pre and post-menopausal women.
- Satisfaction with treatment outcome measured on a 5-point Likert scale. Specific statements about the experience and the acceptability of the treatment and the beliefs about the value of the treatment will be elicited from the participants.

- Surgical intervention (hysterectomy or endometrial ablation)
- Adherence to trial treatments, as reported by the participant.
- Serious adverse events and reactions reported by participants, principally those that are serious and detailed in the respective Summary of Product Characteristics (SmPC) and those that are unexpected.
- Clinical measurements to observe safety and efficacy will include serum haemoglobin, oestradiol as appropriate, pelvic ultrasound (endometrial appearance; fibroid volume) and endometrial biopsies (reported according to pre-agreed criteria by independent pathologists blinded to treatment allocations).

2.2.3 Functional and mechanistic outcomes

- Impact on endometrial tissue architecture including regulation of the vascular compartment
- Impact on endometrial steroid responsiveness, proliferation, survival and inflammatory processes
- Expression of genes implicated in pre-malignant change including tumour suppressors
- Effects on uterine/ fibroid structure and vascularity as determined by MRI-DCE and high resolution structural MRI

3 STUDY DESIGN

3.1 DESIGN

A multicentre, randomised controlled trial of UPA compared to LNG-IUS with a concurrent mechanistic evaluation of UPA. A trial schema is shown in Appendix 2.

4 STUDY POPULATION

The target population is women who present to primary and secondary care with HMB. Participants will be recruited from the gynaecological, out-patient clinics of participating centres, fitting around their current service provision. Recruitment will be supported by dedicated research nurses, who will work with local gynaecology leads. A flowchart of the recruitment process is shown in Figure 1.

4.1 NUMBER OF PARTICIPANTS

UCON will aim to recruit a minimum of 220 women into the randomised controlled trial and from those, approximately 20 women will be required to undergo more detailed evaluation to contribute to the mechanistic study which is conducted at the Royal Infirmary of Edinburgh. The statistical basis of the sample size calculation is detailed in Section 9.1.

Recruitment will take place over 24 months from 5 centres (i.e. 2 participants/ centre/month).

4.2 ELIGIBILITY

In order to be randomised into the UCON trial, all eligibility criteria must be satisfied. Investigators will be asked to confirm each eligibility criteria at randomisation.

4.2.1 Inclusion Criteria

- Aged 18 years or over
- Menstrual bleeding that she perceives to be heavy and troublesome
- Willing to receive medical treatment with either UPA or LNG-IUS
- Willing to undergo two pelvic ultrasounds
- If allocated to UPA, willing and eligible to undergo two endometrial biopsies with the possibility of a third and fourth (i.e. up to four biopsies)
- If allocated to UPA mechanistic sub-study, willing and eligible to undergo three endometrial biopsies with the possibility of a fourth and fifth (i.e. up to five biopsies). If 'No' may be randomised to RCT if UPA endometrial biopsy consent given
- Willing to use barrier contraception if allocated to UPA
- Given written informed consent
- Willing and eligible to undergo up to three magnetic resonance imaging scans? If allocated to UPA, mechanistic sub-study only. If 'No' may still be randomised to RCT

4.2.2 Exclusion Criteria

- Post-menopausal
- A >14 week fibroid uterus and/or cavity length >11 cm confirmed by ultrasound scan
- Submucosal fibroids >2cm diameter confirmed by ultrasound scan
- Contraindications to UPA or LNG-IUS
- Intention to continue current use of Cytochrome P450 (CYP3A4) inhibitors
- Intention to continue current use of Cytochrome P450 (CYP3A4) inducers (e.g. Phenytoin, carbamazepine, rifampicin, St John's Wort)
- Intention to continue current use of P-glycoprotein substrates (e.g. digoxin)
- A past, current or suspected diagnosis of endometrial hyperplasia or neoplasia
- Severe hepatic impairment
- Epilepsy managed with carbamazepine, phenytoin
- Significant renal impairment
- Pregnant
- Current plans to become pregnant within 12 months
- Currently breastfeeding

- Severe asthma that is not sufficiently controlled by oral glucocorticoids
- Past or current known history of with uterine, cervical, ovarian or breast cancer.
- Current use of progestagen-releasing intrauterine device (except if allocated within UCON)
- Intention to continue regular use of Mefenamic acid
- Intention to continue regular use of Tranexamic acid
- Intention to continue regular use of GnRH analogues
- Intention to continue regular use of Progestagen-only contraceptive
- Intention to continue regular use of any combined oral contraceptive pills
- Intention to continue regular use of hormonal replacement therapy

4.2.3 Exclusion of particular populations

Renal impairment is not expected to significantly alter the elimination of UPA. In the absence of specific studies, UPA is not recommended for patients with severe renal impairment unless the patient is closely monitored.

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

UPA use in women with severe asthma insufficiently controlled by oral glucocorticoids is not recommended.

4.3 CO-ENROLMENT

Women randomised to the UCON trial should be excluded from participation in any further trial of investigational medicinal products (IMPs) for the treatment of gynaecological disorders or infertility. If the woman has withdrawn from the trial treatment but is still contributing to data collection, any further treatments within trials for her HMB should be noted, for example if she chooses to participate in a trial of surgery for HMB.

Women already participating in another trial of an IMP for a non-gynaecological reason are able to participate in UCON, provided careful consideration of the interactions between that IMP and the UCON trial treatments is undertaken. Arrangements for co-enrolment with another CTIMP will be bound by a written agreement between the Chief Investigator and Co-Sponsors of both/all CTIMPs implicated. This agreement will include special safety reporting measures if required; a minimum wash-out period between last dose in one study and first dose in another; a statement to indicate that the chairs of the TSC/DMC from each study and statisticians form each study that they have no objections to the proposals for co-enrolment; and a statement that arrangements for attribution of liability for co-enrolled participants have been put in place agreed between the sponsors of both/all CTIMPs implicated.

5 PARTICIPANT SELECTION AND ENROLMENT

5.1 IDENTIFYING PARTICIPANTS

Patients will be recruited from the gynaecological, outpatient clinics of participating centres (identified in both primary and secondary care), fitting around their current service provision. Figure 1 shows the different routes by which women may be identified and approached.

5.1.1 Identification from GP databases

Patients with a recent history of HMB problems may be identified within GP practices. Databases will be screened using the HMB related read codes, with access to these patient identification centres negotiated via the local Primary Care Network. The hospital will send potentially eligible women a patient invitation letter, a copy of the participant information sheet and be invited to contact the UCON research nurse to discuss the trial and/or make a hospital appointment.

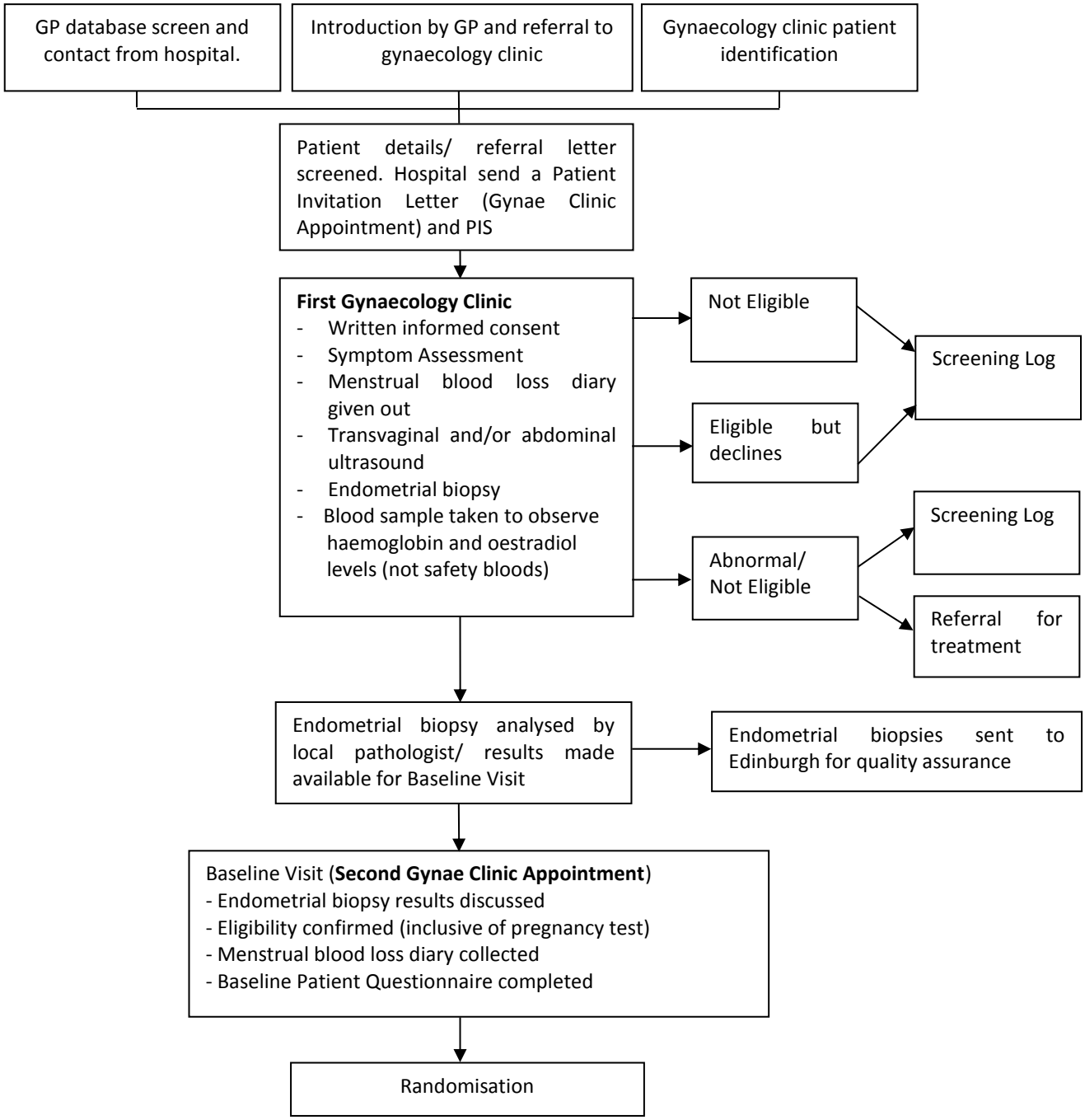
5.1.2 GP Referral to Secondary Care

Patients with existing HMB problems who present to a GP may then be referred to a participating hospital. GP practices in the catchment area of the participating centres will be made aware of the study and will be encouraged to discuss the trial with the woman, explaining a referral will be necessary. The UCON research nurse(s) will screen all patient referral letters to identify referred participants who have been introduced to the trial and arrange a gynaecology clinic appointment.

5.1.3 Gynaecology Clinic Patient Identification

The UCON research nurses will screen the patient referral letters who have been referred by their GP to secondary care but who have not been introduced to the trial. Eligible patients will then receive a patient invitation letter along with a copy of the participant information sheet and be invited to contact the UCON research nurse to discuss the trial and/or make a hospital appointment.

Figure 1: Identification and screening of participants for the UCON trial



5.2 CONSENTING FOR SCREENING FOR ELIGIBILITY

All women who are referred to secondary care with HMB will be identified by the UCON research nurse(s) in each centre as a potential participant, prior to her outpatient appointment. The gynaecologist who will be providing her clinical care will discuss treatment options and establish eligibility based on history and preferences. The option to contribute to the mechanistic sub-study will instead be discussed in those centres able to contribute to the sub-study. Women who are

confirmed pregnant are not eligible for the trial and participants would need to be prepared to avoid pregnancy for one year, so a discussion must be held about intentions to conceive.

Consent to participate in UCON will be sought by the gynaecologist, and/ or by a research nurse. Women will be asked to consent to the UCON Trial in order that trial specific procedures, namely endometrial assessment using transabdominal and/ or transvaginal ultrasound and outpatient endometrial biopsy, can be undertaken. Women will be asked to confirm their consent by initialling the appropriate boxes on the consent form and signing in the presence of the person taking consent. Multiple copies will be available to ensure a copy is given to the women, one is kept in the patient notes, one in the local site file and one is sent to the UCON Trial Office.

Women who consent at this point should have the ultrasound(s) performed and biopsy taken at the same clinic appointment if at all possible. All women should be given a menstrual blood loss diary containing the PBAC to take away and complete during their next period, which ideally will occur before the next gynaecology clinic appointment. The completed blood loss diary will need to be returned at the baseline visit prior to randomisation.

At the Royal Infirmary of Edinburgh the option of participating in addition in the mechanistic sub-study and undergoing additional endometrial biopsies and/ or MRI scans should be discussed. Women should be advised that these additional assessments are only applicable if they are randomly allocated to UPA.

All women approached should be recorded on the screening log(s), available in the investigator site file. This information will only be passed to the coordinating centre as an anonymous screening log.

5.3 CONFIRMATION OF ELIGIBILITY BEFORE RANDOMISATION/ ENTRY INTO THE MECHANISTIC SUB-STUDY

The participant should be invited to a baseline (second) gynaecology clinic appointment by which time the results of the endometrial biopsy must be available. Normal findings from the local histopathology service will confirm eligibility for UCON, which should be relayed to the woman and continued consent established. At this point, the menstrual diary should be collected, if the woman has had a period in between appointments, and the other baseline questionnaires should be completed in clinic at this time.

Any pathological or suspicious findings from the biopsy should be investigated thoroughly and treated as appropriate outside of the UCON trial.

5.4 INELIGIBLE AND NON-RECRUITED PARTICIPANTS

If a woman is screened but is not eligible for the trial due to a preference, contraindication or pathological reason for their HMB, or consent for randomisation is not given, an anonymous record of the case should be kept in the screening log. The screening log will include, age group, ethnic group, and the reason each patient not eligible for the trial. Women who consent and have an ultrasound and endometrial biopsy but are then found to be ineligible will be noted. The screening log should be kept in the site file and a copy sent to the UCON Trial Office, who will be unable to identify women based on the information provided. This screening log information will inform updates to the funder regarding recruitment targets for UCON.

5.5 RANDOMISATION

5.5.1 Randomisation Procedures

Immediately after eligibility has been established, baseline questionnaires have been completed, and once written informed consent has been obtained, the women may be randomised into the trial.

The Birmingham Clinical Trials Unit will provide third part web-based randomisation with telephone back-up. Patients are entered and randomised into the trial by logging into secure online randomisation available at https://www.trials.bham.ac.uk/UCON. Each centre and each randomiser will be provided with a unique log-in username and password in order to randomise a patient online. The online randomisation is available 24 hours a day, 7 days a week apart from short periods of scheduled maintenance and occasional network problems. Alternatively, investigators can make one Freephone telephone call (Tel - 0800 953 0274) to the randomisation service. Telephone randomisations are available Monday-Friday, 09:00-17:00.

Clinical Assessment and Randomisation Forms will be provided to investigators and may be used to collate the necessary information prior to randomisation. All eligibility related questions and data items on the Clinical Assessment and Randomisation Form will need to be answered before a trial number can be given. Only when all eligibility criteria and baseline data items have been provided will a trial number and treatment allocation be given followed by a confirmatory email sent to the randomising investigator, local Principal Investigator, local pharmacist and the research nurse.

A minimisation procedure using a computer based algorithm will be used to avoid chance imbalances in treatment allocation and the following potentially important variables:

Age: ≤35yrs or >35yrs
BMI: ≤25 kg/m^2 or >25 kg/m^2
Presence of any fibroid >2cm, as determined by the ultrasound scans
Duration of symptoms: < 1year or ≥1 year
Site: Individual Site
Agreement to enter sub-study: Both/ MRI only/ Biopsy Only/ Neither and N/A

In addition, to avoid any possibility of the treatment allocation becoming too predictable, we will include a random factor within the algorithm in which for a proportion of the allocations (1 in 5) true randomisation will be implemented rather than by using the minimised allocation.

5.5.2 Treatment Allocation

Participants will be randomised individually into the UCON trial in an equal ratio to either ulipristal acetate (UPA) or levonorgestrel releasing intrauterine system (LNG-IUS).

Figure 2: Patient pathway (Sites except Royal Infirmary of Edinburgh)

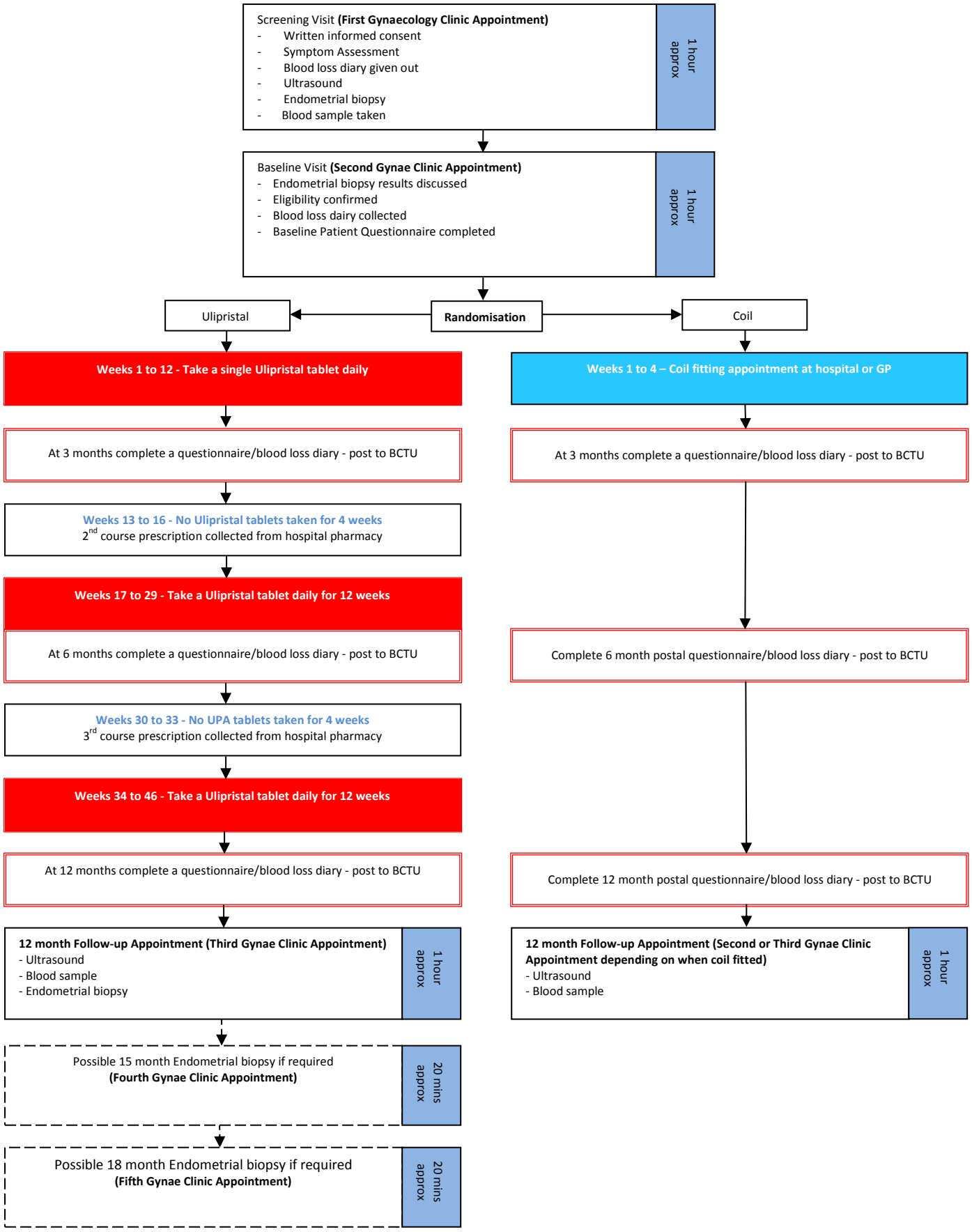
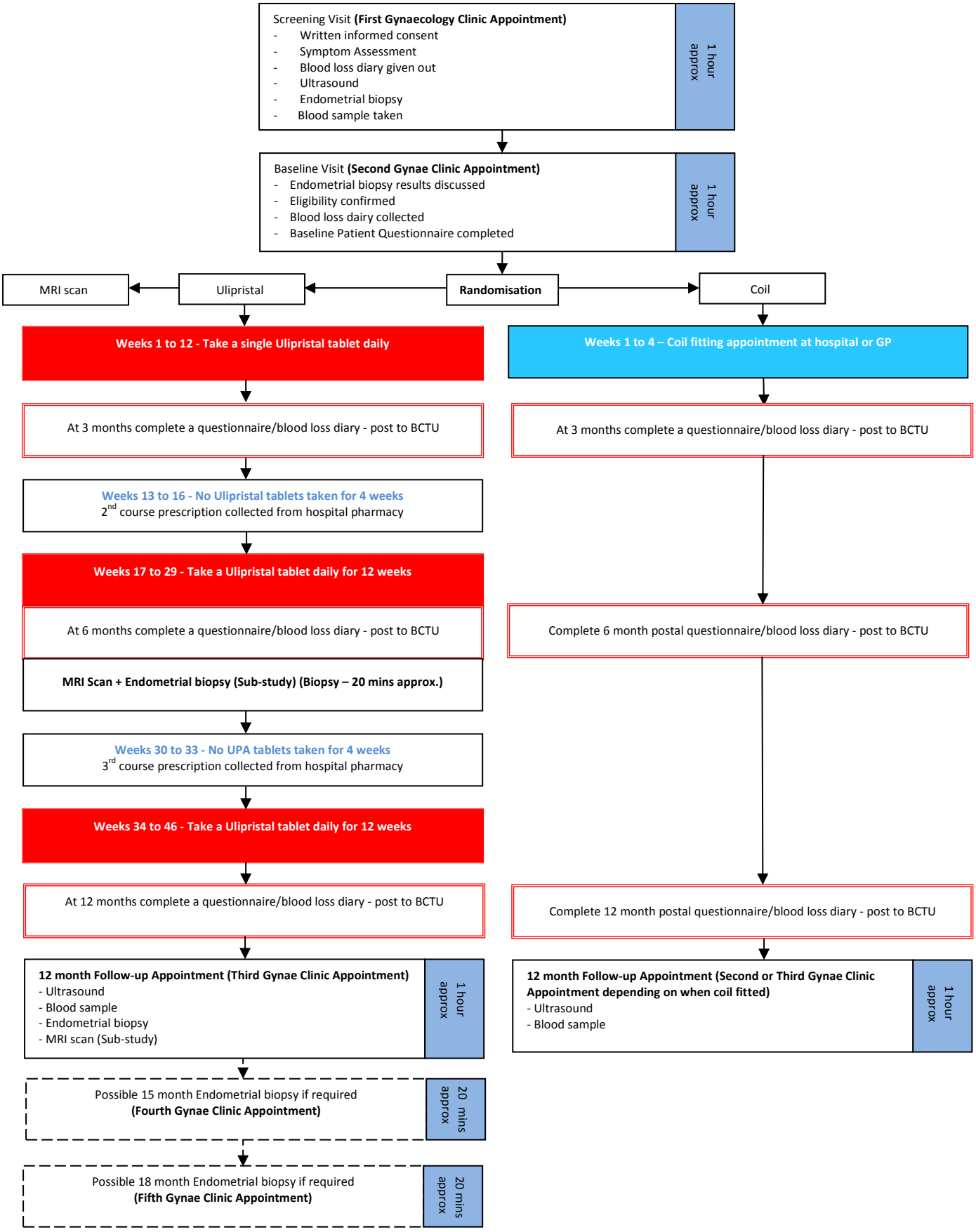


Figure 3: Patient pathway (Royal Infirmary of Edinburgh only)



5.5.3 Baseline MRI for women in mechanistic sub-study (UPA)

Women opting for the mechanistic sub-study at the Royal Infirmary of Edinburgh will, have additional assessments that relate to this study only, but will otherwise complete the same study outcome as those randomised to the UPA group and be followed up in exactly the same manner. As part of the additional assessments will, where possible undergo an MRI scan during the secretory phase (second half of her cycle) of her menstrual cycle before commencing UPA (see Figure 3).

5.5.4 Blinding and Emergency Unblinding Procedures

As the treatments are so different in route of administration, the participants, investigators, research nurses and other attending clinicians cannot be blinded to the treatment allocation.

5.5.5 Withdrawal of Study Participants

Trial treatment should continue until a woman has reached the 12 month post-randomisation unless:

- A known serious adverse reaction to UPA occurs and in the opinion of the investigator or clinical that it is medically necessary to withdraw the woman from trial treatment.
- A suspected unexpected serious adverse reaction occurs
- A participant changes mind and wishes to become pregnant
- The participant refuses to take the trial drug
- Women allocated LNG-IUS can retain the coil *in situ* for up to 5 years if they wish (depending on the product and manufacturer), and can have the coil replaced after this

With premature cessation of trial treatment, the trial staff will make every responsible effort to obtain, and record, information about the reasons for discontinuation, any adverse events and to follow-up the women for all safety and efficacy outcomes, as appropriate. A second endometrial biopsy for women ceasing UPA treatment should be arranged.

A participant may voluntarily withdraw participation in this study at any time. If a participant does not return for a scheduled visit or return a postal questionnaire, responsible attempts will be made to contact her and where possible, complete the patient reported outcome measures, and review compliance and adverse events. If a woman decides, after randomisation, she does not wish to take UPA, or wishes to have the LNG-IUS removed or wishes to withdraw from the trial for any reason (e.g. wishes to conceive or no longer interested in the research) then the woman should be strongly advised to have a second endometrial biopsy taken, four weeks after cessation of UPA. All participants wishing to withdraw from the trial will have the option of withdrawing from all aspects of the trial but may allow for continued use of data collected up to that point.

Where possible, the centre and study team will aim to document the reason for withdrawing from the trial. Clear distinction will be made as to whether a participant is withdrawing from trial treatments whilst allowing further follow-up, or whether the participant refuses any follow-up. If a participant explicitly withdraws consent to have any further data recorded their decision will be respected and recorded. All communication surrounding the withdrawal will be noted in the patient's hospital records and in the trial database and no further data will be collected for that participant.

The target sample size of 220 patients includes a 20% loss to follow-up rate. Rates will be monitored to detect differential drop-out, which can bias clinical trial results and reduce the power of the trial to detect important differences.

6 INVESTIGATIONAL MEDICINAL PRODUCT(S)

6.1 STUDY DRUG

6.1.1 Study Drug Identification

The investigation medicinal products (IMPs) are ulipristal acetate and levonorgestrel-releasing intrauterine system will be used as a reference in its authorised form.

6.1.2 Ulipristal acetate (Comparator)

UPA is provided as a 5mg tablet. The trade name for UPA in the European Union is Esmya**™** for treatment of uterine fibroids, and is marketed by Gedeon Richter.

6.1.3 Levonorgestrel (Reference)

The LNG-IUS is a contraceptive device that slowly releases a daily dose of 20 µg levonorgestrel into the uterine endometrium. It is a long acting reversible contraceptive preparation that requires removal and reinsertion every five years. LNG-IUS is approved for use as a contraceptive and for HMB and in the context of the current trial is manufactuered by two companies. Bayer Pharma AG market their LNG-IUS under the name of Mirena**™** and Actavis UK Ltd under the name of Levosert.

6.1.4 Study Drug Manufacturer and Supply

Each centre pharmacy will arrange an initial and continuing supply of ulipristal acetate and LNG-IUS through normal procurement procedures.

6.1.5 Marketing Authorisation Holder

The marketing authorisation holder for UPA (Esmya™) is Gedeon Richter (Hungary) Plc and the marketing authorisation number(s) is EU/1/12/750/001. The ATC code is G03XB02.

The marketing authorisation holder for LNG-IUS (Mirena™) is Bayer Plc and the marketing authorisation number(s) is PL00010/0547. The ATC code is G02BA03.

The marketing authorisation holder for LNG-IUS (Levosert) is Actavis UK Ltd and the marketing authorisation number(s) is PL30306/0438. The ATC code is G02BA03.

6.1.6 Labelling and Packaging

All details of trial drug supply; labelling, storage and preparation are as per the requirements of the Medicines for Human Use (Clinical Trials) Regulations 2004 and are detailed in the UCON Pharmacy Manual which is supplied to pharmacy at the time of site approval.

UPA dispensed by the pharmacy will require a trial specific label, complying with the Annex 13 of the EU Directive on Clinical Trials, 2004. Supplies of labels will be provided to the pharmacy at each participating hospital.

As LNG-IUS is not dispensed and is fitted according to the manufacturer's recommendations, so it will therefore not require trial specific labelling.

6.1.6 Storage

The UPA tablets must be kept in the blisters in the outer carton in order to protect from light. The blister packs are Alu-PVC/PE/PVDC blister and a pack may contain 28 or 84 tablets. There are no recommendations regarding temperature control of UPA, and so no specific temperature monitoring measures are required for the UCON Trial. The shelf life of UPA is 3 years.

Storage considerations are not applicable for LNG-IUS.

6.1.7 Dispensing and accountability

At randomisation, the first packet of tablets will be dispensed to the woman. The pharmacist will receive notification of the name and trial number of the randomised woman and will prepare the trial treatment tablets for labelling and dispensing. The packet of UPA will contain 12 weeks' supply for use by one participant. An accountability log will be provided to record the dispensing of trial treatment.

6.1.8 Summary of Product Characteristics

The reference document to be used to assess expectedness against the IMP is the Summary of Product Characteristics (SmPC) for that IMP. SmPCs for each IMP can be accessed via the electronic Medicines Compendium (eMC) which contains up to date, easily accessible information about medicines licensed for use in the UK. Please see Appendix 1 for the SmPC for use in the current DSUR reporting period. The SmPC will be provided in the site file and Pharmacy file.

6.2 DOSE AND DELIVERY OF IMPS

6.2.1 UPA

Those allocated to UPA will receive proprietary ulipristal acetate 5mg, orally, once daily.

A single tablet must be taken orally once daily with or without food, at approximately/ or as close as possible to the same time each day. The participant should start taking UPA within the first five days of starting their menstrual bleeding.

If a participant misses a dose, she should take UPA as soon as possible. If the dose was missed by more than 12 hours, the participant should not take the missed dose and simply resume the usual dosing schedule.

Women will be instructed to take UPA in 3 courses according to the following cyclical regime (± 5 days):

1. One 5mg tablet of UPA to be taken daily for 12 weeks then stopped for 4 weeks, when light vaginal bleeding may occur (withdrawal bleed).

2. After 4 weeks off treatment, regardless of whether they experience a withdrawal bleed, they should recommence UPA 5mg daily for another 12 weeks, then stop for 4 weeks, when they will expect to have a withdrawal bleed.

3. Repeat as for treatment courses (2).

We have chosen this regime as women and their clinicians will likely prefer a regime that has only one menstrual bleed between treatment courses and thus our study will be able to provide valuable data on this aspect of UPA treatment.

6.2.2 LNG-IUS

The fitting of the LNG-IUS should be performed by the gynaecologist during outpatient visit, or later by a GP or at a sexual/ reproductive health clinic. If LNG-IUS is fitted within seven days of the onset of menstruation or withdrawal bleeding it will provide immediate contraceptive cover, otherwise barrier methods must be used for 14 days. The LNG-IUS can remain *in situ* up to for 5 years and should be removed by a competent practitioner, with immediate replacement if desired.

6.3 DOSE CHANGES

Each women randomised to UPA will take UPA 5mg, orally, once daily in 3 courses according to the cyclical regime stated in section 6.2.1:

The participant should start taking UPA within the first five days of starting their menstrual bleeding or between 4 week and weeks 5 days from coming off treatment.

6.4 PARTICIPANT COMPLIANCE

6.4.1 Maximising adherence of women to their allocated treatment.

We will try to avoid women not commencing the allocated treatment firstly by careful counselling with respect to childbearing intentions. Randomised women will either be provided with their UPA prescription immediately, or we will encourage women to have the LNG-IUS fitted promptly by the gynaecologist at the baseline clinic visit. To maintain adherence, women in the LNG-IUS group will be counselled to expect some disturbance to their menstrual cycle, but encouraged to persist. In the UPA group, women will receive a reminder to remind them to collect their repeat prescriptions from the hospital pharmacy.

6.4.2 Monitoring compliance

Follow-up questionnaires will ask for self-reported compliance to the allocated treatment. We may also collect data on adherence via a text message at various time points. LNG-IUS drug compliance will be participants who have had the coil fitted within 5 weeks post-randomisation.

UPA compliance will be those participants who report in the follow-up questionnaire to have taken the drug for at least 5 days per week. UPA drug compliance may also be evaluated by 'pill-counting'.

6.5 SPECIAL WARNINGS AND PRECAUTIONS FOR USE FOR ULIPRISTAL ACETATE

There is the potential for other medicinal products to affect ulipristal acetate and conversely the potential for ulipristal acetate to affect other medicinal products. For further details regarding guidance on prohibited and permitted medications please see sections 6.9.1and 6.9.2. For guidance regarding the potential interactions with other medications please see section 6.5.3.

6.5.1 Overdose

Experience with ulipristal acetate overdose is limited. Single doses up to 200 mg and daily doses of 50 mg for 10 consecutive days were administered to a limited number of subjects, and no severe or serious adverse reactions were reported (please see Appendix 1 for the Ulipristal Acetate SmPC).

6.5.2 Contraception

Concomitant use of UPA with 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 ulipristal acetate are anovulatory, where contraception is required, the woman will be asked to use a barrier method with spermicidal foam/gel/film/cream/suppository, in line with MHRA contraception guidelines.

6.5.3 Potential drug interactions

Ulipristal acetate is not recommended for patients receiving P-glycoprotein (P-gp) substrates (e.g. dabigatran etexilate, digoxin).

Co-administration of moderate or potent Cytochrome P450 (CYP3A4) inhibitors (e.g. erythromycin propionate, ketoconazole, ritonavir, nefazodone) may lead to significant changes in plasma levels of ulipristal acetate and so women requiring potent drugs are not eligible for UCON and the use of UPA in those requiring moderate potency CYP should be review carefully. Concomitant use of mild CYP3A4 inhibitors is acceptable and no dose adjustment of UPA is considered necessary.

Patients receiving concomitant Cytochrome P450 (CYP3A4) inducers may have reduced plasma levels of UPA and so concomitant use potent CYP3A4 inducer, such as anti-convulsants (e.g. carbamazepine, phenytoin) or anti-infectives (e.g. rifampicin, nevirapine) or St John's Wort is not recommended.

6.6 KNOWN ADVERSE REACTIONS FOR ULIPRISTAL ACETATE

A full list of known adverse reactions for UPA is given in Table 3, whilst specific issues of concern are detailed here.

6.6.1 Endometrial changes

In 10-15% of women, thickening (> 16 mm by ultrasound or MRI at end of treatment) of the endometrium may occur. In addition, changes in the histology of the endometrium (PAECs) may be observed, that are different to endometrial hyperplasia. These changes are reversible after treatment cessation. More evidence regarding PAEC is discussed in Section 1.2.

6.6.2 Bleeding pattern

Participants 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, participants should notify their GP. Menstrual periods will generally return within 4 weeks after the end of the treatment course.

6.6.3 Other hormonal adverse events

Hot flushes were reported by 12.7% patients on average but the rates varied across trials. In PEARL II, the rates were 24% (10.5% moderate or severe) for UPA and 60.4% (39.6% moderate or severe) for leuprorelin-treated patients. In PEARL I, the rate of hot flushes was 1.0% for UPA and 0% for placebo.

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.

6.7 SPECIAL WARNINGS AND PRECAUTIONS FOR USE FOR LEVONORGESTREL

6.7.1 Fitting of the LNG-IUS

LNG-IUS fitting should ideally be performed by an experienced gynaecologist at the second clinic appointment. If this is not possible, a prescription can be given to enable the woman to go to a sexual health clinic or her GP, for the coil to be fitted by a clinician.

Perforation of the uterine corpus or cervix may occur, most commonly during insertion. This may be associated with severe pain and continued bleeding. If perforation is suspected the system should be removed as soon as possible and reported as a trial treatment withdrawal to the UCON Trial Office.

The insertion tube for LNG-IUS has been designed to minimise the risk of infections. Women should be told to be aware of symptoms and signs suggestive of pelvic infection and to go to her GP if at all concerned.

The RCOG guidelines suggest a women should be re-examined six weeks after insertion and further examinations should be performed where clinically indicated, but this will be left to the discretion of the gynaecologist to advise.

6.7.2 Potential drug interaction

The metabolism of progestogens may be increased by concomitant use of CYP3A4 inducers but the influence on these drugs on the contraceptive efficacy of the LNG-IUS has not been studied. However, it is not believed that CYP3A4 inducers will have a major importance, due to local mechanism of action of LNG-IUS.

6.8 KNOWN ADVERSE REACTIONS TO LEVONORGESTREL

Undesirable effects are more common during the first months after the insertion, and subside during prolonged use. A full list of known adverse reactions for LNG-IUS is given in Table whilst specific issues of concern are detailed here.

6.8.1 Bleeding irregularities

LNG-IUS usually achieves a significant reduction in menstrual blood loss in 3 to 6 months of treatment. Irregular bleeding/spotting may occur during the first months of therapy in pre-menopausal women. Some women's periods may even stop completely. Increased menstrual flow or unexpected bleeding may be indicative of expulsion.

6.8.2 Possibility of pregnancy

The LNG-IUS, when inserted properly, is an extremely effective contraceptive. The possibility of pregnancy should be considered in amenorrhoeic women if there are other symptoms, and expulsion should be excluded.

The absolute risk of ectopic pregnancy in LNG-IUS users is low. However, when a woman becomes pregnant with the LNG-IUS in situ, the relative likelihood of ectopic pregnancy is increased. The possibility of ectopic pregnancy should be considered in the case of lower abdominal pain - especially in connection with missed periods or if an amenorrhoeic woman starts bleeding.

6.9 OTHER MEDICATIONS

6.9.1 Permitted Medications

Drugs not listed as prohibited or have potential to interact (see Sections 6.5.3 and 6.7.2) are allowed.

6.9.2 Prohibited Medications

In order not to confound the effects of the trial treatments, the following should not be prescribed or taken by any participants whilst on trial treatment. Should the women withdraw or be excluded from the trial treatment but continue to provide data, continued regular use of below drugs should be noted. For patients who are 'coming off' some medications pre-randomisation then please refer to the wash out times specified in section 6.9.3.

- Mefenamic acid
- Tranexamic acid
- GnRH analogues

- Progestagen-only contraceptive
- Any progestagen-releasing intrauterine device (except if allocated within UCON)
- Any combined oral contraceptive pills

6.9.3 Wash out times

• GnRH agonist/ antagonist: 3 to 6 month sustained-release preparation	52 wks
• Immediate or monthly sustained-release GnRH agonist preparation	26 wks
• Sex steroid: Progestins (systemic/ progestin-releasing intra-uterine system)	4 wks
• Oral contraceptive	4 wks
• Mefenamic acid or antifibrinolytic drugs such as tranexamic acid	1 wk

7 STUDY ASSESSMENTS

Due to the different nature of the IMPs, the timing and format of the study assessments will differ slightly between the groups.

7.1 STUDY ASSESSMENTS OVERVIEW

A summary of actions and assessments undertaken, and data collected, at each time point is shown in **the Trial Schema (Appendix 2)**. Women who have consented and randomised to the mechanistic sub-study will have additional assessments that relate to this study only, but will otherwise complete the same study outcome as those randomised to the UPA group and be followed up in exactly the same manner.

7.2 TIMING OF STUDY ASSESSMENTS

The overriding principles for the timing of the follow-up study assessments are:

1. The patient completed questionnaires should ideally be completed in the final week of each on-treatment cycle for the UPA group, and at an equivalent time for the LNG-IUS group.

2. The menstrual blood loss diary whilst on treatment should ideally be completed over the final four weeks of each treatment cycle in the UPA group, and at an equivalent time for the LNG-IUS group. The UPA group will also be asked to complete the diary during the first 4 weeks off treatment before the start of the next treatment cycle (as per the cyclical regime stated in section 6.2.1).

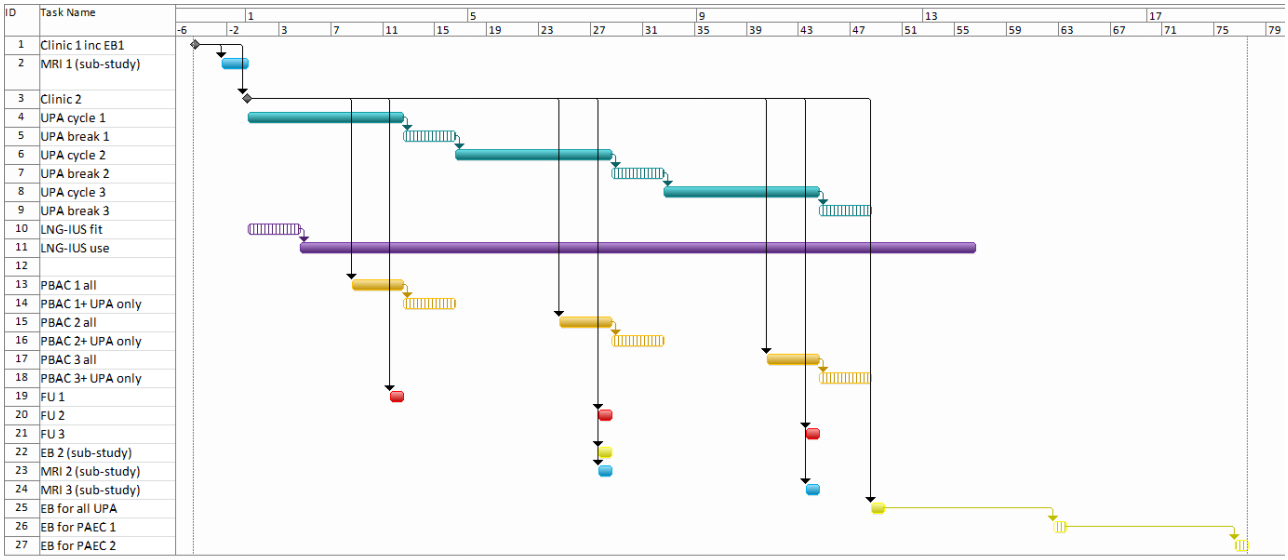
3. The post-treatment endometrial biopsy should be completed after 4 weeks off treatment, which would be approximately 48 weeks after UPA was commenced.

4. Should PAECs be observed in the post-treatment biopsy specimen in the UPA group, a repeat endometrial biopsy should be taken around 13 weeks after the completion of treatment, and then again around 26 weeks post-treatment if PAECs persist.

5. The endometrial biopsy and MRI at time point 26 weeks in the sub-study should be in the final week of the second UPA cycle, to determine the features of the endometrium while receiving treatment.

A timeline for the treatment regimens and completion of the assessments is shown in Figure 4.

Figure 4: Timeline for the treatment regime for UPA and LNG-IUS, and study assessments.



Key: EB endometrial biopsy; FU patient questionnaire

7.3 OUTCOMES COLLECTED AT STUDY ASSESSMENTS

Table 1 shows the outcomes collected at each time point in the UCON trial and mechanistic sub-study.

Table 1: Schedule of outcome assessment for UCON trial and mechanistic studies

(X) optional ((X)) dependent upon endometrial assessment at previous time point

Timepoint	Screening (1)	Baseline (2)	3 months (approx) (3)	6 months (approx) (4)	12 months (approx) (5)	Post-treatment 1 (6)	Post-treatment 2 (7)
Written informed consent	X						
Patient questionnaires (MMAS, UFS-QOL, SAQ, other patient reported outcomes, compliance and adverse events)		X	X	X	X		
Menstrual bleeding diary	X		X	X	X		
Blood sample, to observe haemoglobin and oestradiol levels (not safety bloods)	X				X		
Ultrasound pelvic assessment	X				X		
Endometrial biopsy	X				X UPA only		
Endometrial biopsy – additional for women in UPA group who exhibit PAEC						((X)) UPA only	((X)) UPA only
Follow up outpatient appointment to discuss post-trial treatment options						(X) UPA only	
Purposive samples 1 and 2 (Edinburgh sub-study only)							
Endometrial biopsy	X			X UPA only	X UPA only	((X)) UPA only	((X)) UPA only
MRI (DCE-MRI and high resolution structural MRI)		X		X UPA only	X UPA (+) only		

(X) optional ((X)) dependent upon endometrial assessment at previous time point

(+) MRI to be performed in final week of treatment

* Endometrial biopsies will be stored at the University of Edinburgh Female Reproductive Tract Tissue Resource (10/S1402/59) and 16/ES/0007.

8 DATA COLLECTION

8.1 DATA COLLECTION FORMS

Data for the purpose of assessing the efficacy and safety within the UCON trial will be collected from the women, her gynaecologist and the histopathologist on a number of data collection (case report) forms.

8.1.1 Participant Questionnaire

The participant questionnaire is a booklet containing a number of validated instruments and questions completely independently by the participant. The booklet at baseline will contain:

- Menorrhagia Multi-Attribute Scale (MMAS)
- Uterine Fibroid Symptom and Quality of Life (UFS-QoL)
- Quality of Life (EuroQoL *EQ-5D-5L)) and (ICECAP-A)*
- Sexual Activity Questionnaire (SAQ)
- Satisfaction with treatment outcome measured on a 5-point Likert scale. Specific statements about the experience and the acceptability of the treatment and the beliefs about the value of the treatment will be elicited from the participants.
- Visual analogue scales for menstruation duration, regularity and pelvic pain

At the three follow-up timepoints, the following additional data will be sought:

- Adherence to UPA dosing schedule, as subjectively reported on an ordinal scale by the participant (for those allocated to UPA).
- Discontinuation or changes in allocated treatment.
- Any hospitalisations, or further investigations or treatments from a gynaecologist.
- Any pregnancies.
- Serious adverse events reported by participants, principally those that are unexpected or are known and relevant to the trial treatments.

The booklet will either be sent out in paper form by post, be emailed as a data-form enabled attachment, be via a password protected web form or be presented to the woman in an outpatient clinic. Various ways in which to contact women (land line and mobile telephone, email, address) will be collected and all may be used in the process of collecting the data.

8.1.2 Menstrual Diary

The standard pictorial blood assessment chart (PBAC) (14) will be given to the woman at the first clinic visit to allow her to complete during her next menstruation and return it at the second clinic visit, which should be scheduled to be at least 4 weeks after the first.

Both UPA and LNG-IUS may induce amenorrhea (absence of bleeding) in some women, so whilst on treatment, the concept of a regular cycle is problematic. A modified menstrual diary, with ordinal questions regarding bleeding each day, will be used to establish the degree of menstrual bleeding. This will be completed for 28 days from week 8 for women in the LNG-IUS group and for 56 days

from week 8 in the UPA group, then again at week 24 and week 40, for 28 and 56 days for the LNG-IUS and UPA groups, respectively.

8.1.3 Clinical Assessment and Randomisation Form

At the first clinic visit, the gynaecological clinical history of the woman will be taken and details of duration of HMB symptoms, previous gynaecological treatment for HMB, and the contraceptive use and needs of the woman will be collected alongside basic demographic details. A blood sample to observe serum haemoglobin and oestradiol levels will be taken and results recorded in the clinical assessment and randomisation form.

8.1.4 Ultrasound Form

A pelvic examination by transabdominal and/or transvaginal ultrasound will be undertaken and cardinal features noted as possible presence of fibroids and uterine size and size of largest fibroid to make the comparison between baseline and 12 month follow-up possible.

8.1.5 Clinical Assessment and Randomisation Form and Screening Logs

The Clinical assessment and Randomisation Form is a checklist for eligibility and key prognostic details needed for minimisation within the randomisation. This is completed by the investigator or UCON research nurse before randomisation.

The Screening Logs, described in Section 5.4, will record basic details of all women approached, including those who are found to be ineligible and those that decline to participate. This should be kept up to date by the UCON research nurse.

8.1.6 Endometrial Biopsy Report Form

The local consultant histopathologist will report on the morphology and cellular architecture of the endometrial biopsy sample on a local report form. The baseline biopsy and the 48 week post treatment biopsy in the UPA group will be assessed using standard techniques to identify PAECs. Independent analysis of the slides taken from the samples by the Lead Pathologist at the University of Edinburgh will be recorded on a standardised report form.

8.1.7 Serious Adverse Event Form

This will collect details of all SAEs are defined and description in Section 10.5.

8.1.8 Mechanistic Study Data Forms

Data forms pertinent to the assays and analyses being undertaken on the endometrial biopsy and MRI scans taken for the sub-study will be used to standardise data collected.

8.2 SOURCE DATA

For the purposes of the UCON trial, source data comprises of:

- Clinical Assessment and Randomisation Form
- Patient questionnaire and menstrual diary
- Clinical notes
- Blood sample for haemoglobin and oestradiol analysis
- Ultrasound
- Endometrial biopsy sample for standard histopathological analysis.

8.3 DATA MANAGEMENT

Data from the Clinical Assessment and Randomisation Form and Endometrial Biopsy Report Form and should be entered on to the secure online UCON database as soon as possible after collection by the research nurse, investigator or histopathologist, who will be allocated personal usernames and passwords that restrict access to participants at their centre. Alternatively, paper forms can be sent to the UCON Trial Office for central input. Patient completed forms will be returned directly to the UCON Trial Office for data entry.

Data validation is built into the online database, so that range, date and logic checks are performed at the point of data entry. Email, text message and letter reminders will be sent to the research nurses or participants for missing data forms, missing data or data inconsistencies.

8.4 QUALITY ASSURANCE OF ENDOMETRIAL BIOPSY ASSESSMENTS

The assessment of endometrial biopsies should be undertaken by a consultant histopathologist with expertise in endometrial analysis. For quality assurance, a second assessment will be undertaken by the lead pathologist for UCON, Professor Alistair Williams at the University of Edinburgh. Slides taken from the samples will be labelled with the trial number and send for second reading in secure shipping containers provided by the UCON Trial Office.

For the baseline endometrial biopsy, the second assessment in Edinburgh will not be used to confirm eligibility for the trial and therefore slides may be sent in batches.

For the final post-treatment biopsy in the UPA group, a local assessment will be under taken and the slides sent promptly to Edinburgh. Whilst the local assessment will be noted, the second Edinburgh review of the slides, undertaken without knowledge of the local assessment, will determine the presence or absence of PAEC for the purpose of the trial. Those women with PAECs as confirmed by Edinburgh will be asked to return for endometrial biopsies at 13 weeks, and if necessary 26 weeks after completion of the final UPA course.

All slides will be returned to their originating hospitals after the second assessment.

8.5 MECHANISTIC SUB-STUDY

8.5.1 Endometrial tissue function

An overview of approach to analysis of tissue-specific impacts of UPA on endometrial tissue function are summarised in Table 2 below. The choice of target endpoints has been informed by studies in our own laboratory that have highlighted the impact(s) of progestins, progestin receptor antagonists and receptor modulators levonorgestrel, mifepristone, asoprisnil) on endometrial tissue function, *examples given but not limited to those end points identified in Table 2* (17-19).

Table 2: An overview of approach to analysis of tissue-specific impacts of UPA on endometrial tissue function

Process	Endpoint	Details of analytical method
Tissue morphology	H&E stain histology, number of mitoses and mitochondria	Analysis by expert pathologist qRT-PCR mitochrondrial markers
Vascular morphology	Endothelial and perivascular cell function/morphology	Double staining for CD31 (endothelial cells) and smooth muscle actin Masson Trichrome staining for collagen
Regulation of cell number	Cell proliferation, apoptosis and autophagy	Immunostaining for Ki67, PH3(proliferation) or cleaved caspase 3, microtubule-associated protein 1 light chain 3 alpha (death/survival), gamma H2AX (senescence)
Steroid hormone signalling	Cell-specific pattern of expression of steroid hormone receptors and steroid metabolizing enzymes	Single and double immunostaining for PR, ERalpha, ERbeta, AR, GR
Inflammation	Immune cell complement and inflammatory mediators	qRT-PCR IL15. Immunostaining for CD56, CD68, neutrophil elastase, mast cell tryptase and pan leucocyte marker CD45
Pre-malignant change	Comparison with normal endometrium and endometrial hyperplasia	qRT-PCR, double fluorescent immunohistochemistry PTEN, E-Cadherin, Snail 1, vimentin, PAX2, telomerase (hTERT)

8.5.2 Uterine and fibroid function

The aim of the MRI sub-study is to investigate the hypothesis that UPA will reduce blood flow and blood volume in the endometrium and myometrium in women with HMB. In particular, dynamic contrast enhanced MRI (DCE-MRI) and high spatial resolution structural MRI will be obtained in a subgroup of 20 women treated with UPA. DCE-MRI, combined with pharmacokinetic modelling, yields quantitative estimates of physiological parameters, including tissue blood flow, blood volume fraction and endothelial permeability, as well as volume fraction of the extracellular extravascular space. Structural MRI provides high resolution images suitable for structural segmentation and radiological evaluation that, when combined with design based stereological analysis (20), yield accurate and precise measurements of uterine and fibroid volume for early assessment of treatment response.

Scanning will be performed at baseline, and at 6 and 12 months following commencement of treatment. Scans will take place during the secretory phase of the menstrual cycle at baseline and in the week prior to the end of the second and third cycles of UPA, weeks 27 and 43 respectively.

Structural images will be evaluated clinically by an experienced radiologist, and stereological analysis performed to determine the volumes of the uterus and of any fibroids. Modern design based stereological methods will measure total volume of endo- and myo-metrial compartments, and volume, type and location of individual fibroids, with mathematically predicted precision, on high resolution MR images.

Dynamic Contrast Enhanced (DCE)-MRI will be used to measure uterine tissue perfusion. Contrast agent concentration is modelled as exchange between the blood plasma and extracellular interstitial spaces, providing maps of tissue blood flow, blood and interstitial volume fraction and artery to tissue delay (i.e. lag) time. DCE-MRI data will be analysed using the well-established adiabatic approximation to tissue homogeneity (AAHT) model, to generate pharmacokinetic maps of blood flow, blood volume and extracellular extravascular volume fraction; these will be used to extract representative values for endometrium, junctional zone, outer myometrium and fibroid tissue.

Both MRI approaches are novel in the context of SPRM administration, so will be piloted in the first patients, who may require repeat scans with a refined protocol.

9 STATISTICS AND DATA ANALYSIS

9.1 SAMPLE SIZE CALCULATION

9.1.1 RCT

The trial has been designed to be able to detect a clinically useful difference in MMAS score between the two groups at twelve months with high power. The ECLIPSE Trial, which evaluated the effectiveness of LNG-IUS against Standard treatment for HMB (21) using MMAS as the primary outcome, demonstrated a difference of 13 points between the groups with a standard deviation of 24 points. This difference considered to be clinically meaningful (22) and is equivalent to approximately 0.5 standard deviations. To detect a difference of this size with 90% power (p=0.05) would require 86 women in each group (172 in total). To allow for a 20% loss to follow-up or pregnancy, the sample size has been inflated to 220 women in total.

9.1.2 Mechanistic sub-study

For the mechanistic evaluation 20 samples would give >90% power (p=0.05) to detect a change from baseline in for example, PH3 immuno-score, in the endometrium assuming similar effect sizes (>1 standard deviation) as to those seen in previous studies of other PRMs (19).

9.1.3 Anticipated recruitment period

Recruitment will take place over a minimum of 24 months from at least 5 centres, with a target of 2 patients/centre/month. All centres have large HMB clinics, are experienced in recruiting to RCTs and the BCTU has a track record of completing RCTs in women's health.

9.2 PROPOSED ANALYSES - RCT

The analysis will be by intention to treat. Every attempt will be made to gather data on all women randomised, irrespective of compliance with the treatment protocol. Appropriate baseline

characteristics, split by treatment group, will be presented for each outcome. Point estimates, 95% confidence intervals and p-values from two-sided tests will be reported. A full Statistical Analysis Plan will be drafted prior to any analysis and provided to independent Data Monitoring and Ethics Committee for review.

9.2.1 Primary analysis

A linear regression model will be used to estimate differences in MMAS responses between the two groups at each time point. Baseline score and the minimisation variables (listed in section 5.5.1) will be included in the model as covariates. The statistical significance of the treatment group variable will be determined by an associated chi-squared test.

9.2.2 Secondary analysis

MMAS scores at three and six months follow-up will be analysed as per the primary analysis. Data from the other continuous measures (UFS-QOL, VAS and SAQ) will be analysed in a similar fashion to the MMAS scores. Further exploratory analysis using a repeated measures model will also be used for these continuous measures to examine differences over all time-points. Bleeding diary scores will be converted into categories including the proportion with amenorrhoea (=0) and heavy bleeding (>=100). They will be analysed using relative risks and chi-squared tests. Time from randomisation to surgery (hysterectomy or endometrial ablation) will be analysed by log-rank test with a Cox Proportional Hazard (PH) model also built if the assumptions of proportionality are met. Other outcome measures (Likert responses, Likert ordinal responses, satisfaction) will be analysed using standard methods (tests for trend, absolute and relative risks). Paired t-tests will be used to examine differences within groups over time.

9.2.3 Sub-group analysis

Subgroup analyses will be limited to the same variables which were used as minimisation variables (see Section 5.5.1). Tests for statistical heterogeneity (e.g. by including treatment group by subgroup interaction parameter in the linear regression model) will be performed prior to any examination of effect estimate within subgroups. Our hypothesis is that UPA may be more effective in older (>35 years) and heavier (BMI>25) women and those who have a presence of fibroid or have experienced symptoms for longer than a year.

9.2.4 Handling missing data and other sensitivity analysis

Every attempt will be used to collect full follow-up data on all women. In particular, the trial team will endeavour to follow-up participants even after protocol treatment violation. It is thus anticipated that missing data will be minimal. Patients with missing primary outcome data will not be included in the primary analysis. This presents a risk of bias. Thus, secondary sensitivity analyses will be performed to investigate the impact of any missing data for the primary, as well as any important secondary outcome. This will include worst (for those randomly missing) and best case assumptions (for those not able to complete the primary outcome as they no longer can have menstrual bleeding, i.e. because they have had a hysterectomy). We will also simulate missing responses using a multiple imputation approach. To explore the sensitivity of the primary MMAS

analysis to any ceiling effects (i.e. a high proportion returning a maximum responses, i.e. no problems with bleeding), a Tobit regression model will also be implemented.

9.2.5 Timing of assessments

An interim report including the analysis of major endpoints will be provided in strict confidence to a Data Monitoring Committee at intervals of at least 12 months, or as to a timetable agreed by the DMC prior to study commencement (see Section 11.4 for further details on trial data monitoring including the use of pragmatic stopping criteria). Final analysis will be performed once all women have completed twelve months follow-up.

9.3 PROPOSED ANALYSES – MECHANISTIC STUDY

Outcomes for the n=20 prospectively studied women biopsied at 6 and 12 months will be compared to each participant's own baseline biopsy as a control. Outcomes (e.g. PH3 immunoscore changes within groups over time) will be analysing using paired t-tests following an appropriate transformation and also by using non-parametric methods (e.g. Wilcoxon signed rank test) for confirmation.

10 ADVERSE EVENTS AND PHARMACOVIGILANCE

The Investigator is responsible for the detection and documentation of events meeting the criteria and definitions detailed below. These tasks may also be delegated to a qualified member(s) of the research team. Assessment of events may be delegated to other suitably qualified physicians in the research team who are trained in recording and reporting adverse events.

Participants will be instructed to contact their investigator at any time after consenting to join the trial if any symptoms develop. In the case of an AE, the Investigator should initiate the appropriate treatment according to their medical judgment.

10.1 DEFINITIONS

An **adverse event** (AE) is any untoward medical occurrence in a clinical trial participant which does not necessarily have a causal relationship with an investigational medicinal product (IMP).

An **adverse reaction** (AR) is any untoward and unintended response to an IMP which is related to any dose administered to that participant.

A **serious adverse event** (SAE), **serious adverse reaction** (SAR). Any AE or AR that at any dose:

- results in death of the clinical trial participant;
- is life threatening*;
- requires in-patient hospitalisation^ or prolongation of existing hospitalisation;
- results in persistent or significant disability or incapacity;

- consists of a congenital anomaly or birth defect;
- results in any other significant medical event not meeting the criteria above.

*Life-threatening in the definition of an SAE or SAR refers to an event where the participant was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe.

^Any hospitalisation that was planned prior to randomisation will not meet SAE criteria.

A suspected unexpected serious adverse reaction (SUSAR) is any AR that is classified as serious and is suspected to be caused by either IMP, that it is not consistent with the information about the IMP in the Summary of Product Characteristics (SmPC).

10.2 IDENTIFYING AES AND SAES

There may be expected and unexpected adverse reactions, which may be minor or serious, associated with UPA and LNG-IUS when used in women affected by HMB. The adverse event profile for LNG-IUS is well defined, as the system has been licenced for over a decade, and hence the collection of expected adverse events is not required. For example, elective admission for LNG-IUS insertion or elective admission for hysterectomy would not need to be classified as a serious adverse event. The focus for safety reporting of UPA is on changes to the endometrium.

Open-ended and non-leading verbal questioning of the participant will be used to enquire about AE/SAE occurrence during each study visit and in postal questionnaires. Participants will also be asked if they have been admitted to hospital, had any gynaecological treatments, used any new medicines or changed concomitant medication regimens. If there is any doubt as to whether a clinical observation is an SAE, the event will be recorded and reported.

AEs and SAEs may also be identified via information from the endometrial biopsy, which will be recorded on the histopathology report form and SAE form if necessary. Untoward findings may incidentally be found in women in the mechanistic study, for example unexpected pelvic masses seen on by MR imaging. These will be reported to the local Principal Investigator who will assess whether they constitute an AE or SAE and the appropriate clinical management will be determined. If any untoward findings meet seriousness criteria they will be subject to onward reporting.

All diagnoses of endometrial cancer, ovarian cancer, cervical cancer, breast cancer or ductal carcinoma must be reported as a SAE.

10.3 RECORDING AES AND SAES

When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g. hospital notes, laboratory and diagnostic reports) related to the event. The investigator will then record all relevant information regarding SAEs on the SAE form (if the AE meets the criteria of serious) and record all unexpected AEs in both groups on the AE log. Expected AEs that do not need to be recorded, unless they meet seriousness criteria, are listed in Table 3 for UPA and Table 4 (Mirena) or Table 5 (Levosert) for LNG-IUS.

Table 3: List of known adverse reactions for UPA

System Organ Class	Adverse reactions		
	Very common	**Common**	**Uncommon**
Psychiatric disorders			Anxiety Emotional disorder
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	Alopecia** Dry skin
Musculoskeletal and connective tissue disorders		Musculoskeletal pain	Back pain
Renal and urinary disorders			Urinary incontinence
Reproductive system and breast disorders	Amenorrhea Endometrial thickening*	Uterine haemorrhage* Hot flush* Pelvic pain Ovarian cyst* Breast tenderness/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

Table 4: List of known undesirable effects for LNG-IUS (Mirena) (SmPC 11th June 2013)

System Organ Class	Common ≥ 1/100 to < 1/10	Uncommon ≥ 1/1000 to <1/100	Rare ≥ 1/10,000 to < 1/1000	Unknown
Immune system disorders				Hypersensitivity including rash, urticaria and angioedema
Psychiatric disorders	Depressed mood/Depression Nervousness Decreased libido			
Nervous system disorders	Headache Migraine			
Gastrointestinal disorders	Abdominal pain Nausea	Abdominal distension		
Skin and subcutaneous tissue disorders	Acne Hirsutism	Alopecia Pruritus Eczema Chloasma/Skin Hyperpigmentation	Rash	
Musculoskeletal, connective tissue and bone disorders	Back pain			
Reproductive system and breast disorders	Ovarian cysts Pelvic pain Dysmenorrhoea Vaginal discharge Vulvovaginitis Breast tenderness Breast pain	Pelvic inflammatory disease Endometritis Cervicitis/ Papanicolaou smear normal, class II	Uterine perforation	
General disorders and administration site conditions	Intrauterine contraceptive device expelled	Oedema		
Investigations	Weight increase			Blood pressure increased

Table 5: List of known undesirable effects for LNG-IUS (Levosert) (SmPC 31st March 2015)

Organ system	**Common** **≥ 1/100 to < 1/10**	**Uncommon** **≥ 1/1000 to <1/100**	**Rare** **≥ 1/10,000 to < 1/1000**	**Unknown**
Psychiatric disorders		Depressive mood Nervousness Decreased libido	Altered mood	
Nervous system disorders		Headache	Migraine	
Gastrointestinal disorders		Abdominal pain Nausea	Abdominal distension	
Skin and subcutaneous tissue disorders		Acne	Alopecia Hirsutism Pruritus Eczema	Rash Urticaria
Musculoskeletal and connective tissue disorders		Back pain		
Reproductive system and breast disorders	Bleeding changes Benign ovarian cysts	Pelvic pain Dysmenorrhoea Vaginal discharge vulvovaginitis Breast tenderness Breast pain	Pelvic Inflammatory disease Endometritis Cervicitis Papanicolaou smear normal, class II	Uterine perforation
General disorders and administration site conditions		Intrauterine contraceptive device expelled	Oedema	
Investigations		Weight increase		

10.4 ASSESSMENT OF AES AND SAES

Seriousness, causality, severity and expectedness will be assessed by the Principal Investigator or another suitably qualified physician in the research team. Cases that are considered serious, possibly, probably or definitely related to either IMP and unexpected (i.e. SUSARs) will be thoroughly investigated.

The Investigator is responsible for assessing each AE. This may be delegated to other suitably qualified physicians in the research team who are trained in recording AEs and recording and reporting SAEs.

The Chief Investigator (CI) may not downgrade an event that has been assessed by an Investigator as an SAE or SUSAR, but can upgrade an AE to an SAE, SAR or SUSAR if appropriate.

10.4.1 Assessment of Seriousness

The Investigator will make an assessment of seriousness as defined in Section 10.1.

10.4.2 Assessment of Causality

The Investigator will make an assessment of whether the AE/SAE is likely to be related to the IMP according to the definitions below.

- Unrelated: where an event is not considered to be related to the IMP.
- Possibly Related: The nature of the event, the underlying medical condition, concomitant medication or temporal relationship make it possible that the AE has a causal relationship to the study drug. The assessment of causality will be made against the reference safety information found in the Section 4.8 of the relevant Summary of Product Characteristics.

The reference safety information i.e. known undesirable effects are detailed in the relevant SmPCs and are also referred to in Section 6.1.8.

Where there are concomitant medications, if the AE is considered to be related to an interaction between the IMP and the other medication, or where the AE might be linked to either the IMP or the other medication but cannot be clearly attributed to either one of these, the event will be considered as an AR. Alternative causes such as nature of the HMB, other risk factors and the temporal relationship of the event to the treatment should be considered and investigated.

10.4.3 Assessment of Expectedness

If an event is judged to be an AR, the evaluation of expectedness will be made based on knowledge of the reaction and the relevant product information documented in the SmPC, and summarised in Table 3 and Table 4.

The event may be classed as either:

Expected: the AR is consistent with the toxicity of the IMP listed in the SmPC.

Unexpected: the AR is not consistent with the toxicity in the SmPC.

10.4.4 Assessment of Severity

The Investigator will make an assessment of severity for each AE/SAE and record this on the SAE form according to one of the following categories:

Mild: an event that is easily tolerated by the participant, causing minimal discomfort and not interfering with every day activities.

Moderate: an event that is sufficiently discomforting to interfere with normal everyday activities.

Severe: an event that prevents normal everyday activities.

Note: the term 'severe', used to describe the intensity, should not be confused with 'serious' which is a regulatory definition based on participant/event outcome or action criteria. For example, a headache may be severe but not serious, while a minor stroke is serious but may not be severe.

10.5 REPORTING OF SAES/SARS/SUSARS

Once the Investigator becomes aware that an SAE has occurred in a study participant, the information will be reported to the ACCORD Research Governance & QA Office **immediately or within 24 hours**. If the Investigator does not have all information regarding an SAE, they should not wait for this additional information before notifying ACCORD. The SAE report form can be updated when the additional information is received. Elective admission for LNG-IUS insertion or elective admission for hysterectomy would not need to be classified as a serious adverse event.

The SAE report will provide an assessment of causality and expectedness at the time of the initial report to ACCORD according to sections 10.4.2, Assessment of Causality and 10.4.3, Assessment of Expectedness.

The SAE form will be transmitted by fax to ACCORD on **+44 (0)131 242 9447** or submitted via email to Safety.Accord@ed.ac.uk. Only forms in a pdf format will be accepted by ACCORD via email.

Where missing information has not been sent to ACCORD after an initial report, ACCORD will contact the investigator and request the missing information.

All reports faxed to ACCORD and any follow up information will be retained by the Investigator in the Investigator Site File (ISF). Details received by ACCORD will be passed on to BCTU in their capacity as Coordinating Centre.

10.6 REGULATORY REPORTING REQUIREMENTS

The ACCORD Research Governance & QA Office is responsible for pharmacovigilance reporting on behalf of the co-sponsors (Edinburgh University and NHS Lothian).

The ACCORD Research Governance & QA Office has a legal responsibility to notify the regulatory competent authority and relevant ethics committee (Research Ethics Committee (REC) that approved the trial). Fatal or life threatening SUSARs will be reported no later than 7 calendar days and all other SUSARs will be reported no later than 15 calendar days after ACCORD is first aware of the reaction.

ACCORD will inform Investigators at participating sites of all SUSARs and any other arising safety information.

An Annual Safety Report/Development Safety Update Report will be submitted, by ACCORD, to the regulatory authorities and RECs listing all SARs and SUSARs.

10.7 FOLLOW UP PROCEDURES

After initially recording an unexpected AE or recording and reporting an SAE, the Investigator should make every effort to follow each event until a final outcome can be recorded or reported. The Investigator should follow each unexpected AE or SAE until the event has resolved, the event is assessed as stable by the Investigator, the participant is lost to follow up, or the participant withdraws consent. Follow up information on an SAE will be reported to the ACCORD office.

If, after follow up, resolution of an event cannot be established, an explanation should be recorded.

In the case of PAECs observed at 12 months in those allocated UPA, the women should be reassessed until an endometrial biopsy confirms the restoration of a normal endometrium.

10.8 PREGNANCY

Pregnancy will be considered an AE if women are compliant with either trial treatment. If a woman withdraws from trial treatment and conceives within 12 months of randomisation, this **will not** be considered an AE. However, the investigator will collect pregnancy information for any female participants while participating in the study. The Investigator will record the information on a Pregnancy Notification Form and submit this to the UCON Trial Office within 14 days of being made aware of the pregnancy. BCTU will follow-up any self-reported pregnancies with the women's GP or gynaecologist. All pregnant female participants will be followed up until the outcome of the pregnancy is known. Details received by the UCON Trial Office will be passed on to ACCORD.

11 TRIAL MANAGEMENT AND OVERSIGHT ARRANGEMENTS

11.1 TRIAL MANAGEMENT GROUP

The trial will be coordinated by a Trial Management Group (TMG), consisting of the Chief Investigator, all other grant holders, the Trial Manager and Edinburgh based research nurse. The TMG will meet regularly, by teleconference or face to face.

11.2 THE UCON TRIAL OFFICE

The Trial Office at the University of Birmingham Clinical Trials Unit (BCTU) is responsible for the day to day management of the UCON Trial. The Trial Manager, based at BCTU, will oversee the study and will be accountable to the Chief Investigator. The Data Manager will be responsible for checking the data forms for completeness, plausibility and consistency. Any queries will be resolved by the Investigator or delegated member of the trial team.

The UCON Trial Office will also be responsible for providing all trial materials, including an Investigator Site File (ISF), with copies of all essential documents, and a trial stationary folders

containing all required printed materials e.g. participant information sheets, consent forms. These will be supplied to each collaborating centre, after relevant local research governance approval has been obtained. Additional supplies of any printed material can be obtained on request. The Trial Office also provides the central randomisation service and is responsible for collection and checking of data (including reports of serious adverse events thought to be due to trial treatment), The Trial Office will help resolve any local problems that may be encountered in trial participation.

11.3 TRIAL STEERING COMMITTEE

A Trial Steering Committee (TSC) will be established to oversee the conduct and progress of the trial. Names and contact details are given on page iii.

The Trial Steering Committee (TSC) provides independent supervision for the trial, providing advice to the Chief and Co- Investigators and the Sponsor on all aspects of the trial and affording protection for patients by ensuring the trial is conducted according to the International Committee on Harmonisation Guidelines for Good Clinical Practice in Clinical Trials.

If the Chief and Co-Investigators are unable to resolve any concern satisfactorily, Principal Investigators, and all others associated with the study, may write through the Trial Office to the chairman of the TSC, drawing attention to any concerns they may have about the possibility of particular side-effects, or of particular categories of patient requiring special study, or about any other matters thought relevant.

The BCTU Trial office will forward TSC meeting minutes to the Sponsor and funder. Terms of reference of the Trial Steering Committee and the draft template for reporting will be agreed at the inaugural meeting.

11.4 DATA MONITORING COMMITTEE

An independent Data Monitoring Committee (DMC) will be established to oversee the safety of participants in the trial. Names and contact details are given on page iii.

If one treatment really is substantially better or worse than any other with respect to the primary outcome, then this may become apparent before the target recruitment has been reached. Alternatively, new evidence might emerge from other sources that any one treatment is definitely more, or less, effective than any other. To protect against this, during the main period of recruitment to the study, interim analyses of the primary outcome and adverse events will be supplied, in strict confidence, to the independent DMC, along with updates on results of other related studies, and any other analyses that the DMC may request. The DMC will advise the chair of the TSC if, in their view, any of the randomised comparisons in the trial have provided both (a) "proof beyond reasonable doubt"[1] that for all, or for some, types of patient one particular treatment is definitely indicated or definitely contraindicated in terms of a net difference in the major endpoints, and (b) evidence that might reasonably be expected to influence the patient management of many clinicians who are already aware of the other main trial results. The TSC can

1 Appropriate criteria of proof beyond reasonable doubt cannot be specified precisely, but a difference of at least p<0.001 (similar to a Haybittle-Peto stopping boundary) in an interim analysis of a major endpoint may be needed to justify halting, or modifying, the study prematurely. If this criterion were to be adopted, it would have the practical advantage that the exact number of interim analyses would be of little importance, so no fixed schedule is proposed.

then decide whether to close or modify any part of the trial. Unless this happens, however, the TMG, TSC, the investigators and all of the central administrative staff (except the statisticians who supply the confidential analyses) will remain unaware of the interim results.

The BCTU Trial office will forward DMC open meeting minutes to the Sponsor and funder. Terms of reference of the Trial Steering Committee and the draft template for reporting will be agreed at the inaugural meeting.

11.5 INSPECTION OF RECORDS

Investigators and institutions involved in the study will permit trial related monitoring and audits on behalf of the sponsor, REC review, and regulatory inspection(s). In the event of an audit or monitoring, the Investigator agrees to allow the representatives of the sponsor direct access to all study records and source documentation. In the event of regulatory inspection, the Investigator agrees to allow inspectors direct access to all study records and source documentation.

11.6 RISK ASSESSMENT

An independent risk assessment will be performed by an ACCORD Clinical Trials Monitor to determine if monitoring is required and if so, at what level. An independent risk assessment will also be carried out by the ACCORD Quality Assurance Group to determine if an audit should be performed before, during or after the study and if so, at what locations and at what frequency.

11.7 STUDY MONITORING AND AUDIT

An ACCORD Clinical Trials Monitor or an appointed monitor may visit the Investigator site prior to the start of the study and/or during the course of the study if required, in accordance with the central monitoring plan.

Investigators and their host Trusts will be required to permit trial-related monitoring and audits to take place by either the ACCORD Clinical Trials Monitor and/or Trial Coordinator as and when required who would require direct access to source data and documents as requested. Risk assessment will determine if audit, by the ACCORD QA group, is required. Details will be captured in an audit plan. Audit of Investigator sites, study management activities and study collaborative units, facilities and 3rd parties may be performed.

The study will also adopt a centralised approach to monitoring data quality and compliance. A computer database will be constructed specifically for the trial data and will include range and logic checks to prevent erroneous data entry. Independent checking of data entry will be periodically undertaken on small sub-samples. The trial statistician will regularly check the balance of allocations by the stratification variables.

Trusts may also be subject to inspection by the Medicines and Healthcare Products Regulatory Agency and/ or by the Research and Development Manager of their own Trust and should do everything requested by the Chief Investigator in order to prepare and contribute to any inspection or audit. Trial participants will be made aware of the possibility of external audit of data they provide in the participant information sheet.

12 GOOD CLINICAL PRACTICE

12.1 ETHICAL CONDUCT

The study will be conducted in accordance with the principles of the International Conference on Harmonisation Tripartite Guideline for Good Clinical Practice (ICH GCP).

A favourable ethical opinion will be obtained from the appropriate REC and local R&D approval will be obtained prior to commencement of the study.

12.2 REGULATORY COMPLIANCE

The study will not commence until a Clinical Trial Authorisation (CTA) is obtained from the appropriate Regulatory Authority. The protocol and study conduct will comply with the Medicines for Human Use (Clinical Trials) Regulations 2004, as amended.

12.3 INVESTIGATOR RESPONSIBILITIES

The local Principal Investigator is responsible for the overall conduct of the study at the site and compliance with the protocol and any protocol amendments. In accordance with the principles of ICH GCP, the following areas listed in this section are also the responsibility of each Investigator. Responsibilities may be delegated to an appropriate member of study site staff. Delegated tasks must be documented on a Delegation Log and signed by all those named on the list prior to undertaking applicable study-related procedures.

12.3.1 Informed Consent

The Investigator is responsible for ensuring informed consent is obtained before any protocol specific procedures are carried out. The decision of a participant to participate in clinical research is voluntary and should be based on a clear understanding of what is involved.

Participants must receive adequate oral and written information – UCON Participant Information and Informed Consent Forms will be provided, with variations for those sites participating in the mechanistic sub-study. The oral explanation to the participant will be performed by the Investigator or qualified delegated person, and must cover all the elements specified in the Participant Information Sheet and Consent Form.

The participant must be given every opportunity to clarify any points they do not understand and, if necessary, ask for more information. The participant must be given sufficient time to consider the information provided. It should be emphasised that the participant may withdraw their consent to participate at any time without loss of benefits to which they otherwise would be entitled.

The participant will be informed and agree to their medical records being inspected by regulatory authorities and representatives of the sponsor(s) but understand that their name will not be disclosed outside the hospital.

The Investigator and the participant will sign and date the Informed Consent Form(s) to confirm that consent has been obtained. The participant will receive a copy of this document and with the original filed in the ISF and copies filed in the participant's medical notes and sent to the Trial Office.

12.3.2 Study Site Staff

The Investigator must be familiar with the IMP, protocol and the study requirements. It is the Investigator's responsibility to ensure that all staff assisting with the study are adequately informed about the trial treatments, protocol and their trial related duties.

Each participating centre should also designate at least one nurse as a UCON research nurse. This person would be responsible for ensuring that all eligible patients are considered for the study, that women are provided with study information sheets, and have an opportunity to discuss the study if required. The nurse will be responsible for ensuring the baseline participant questionnaire is completed and for randomisation.

A Delegation Log will be prepared for each site, detailing the responsibilities of each member of staff working on the trial.

12.3.3 Data Recording

The Principal Investigator is responsible for the quality of the data recorded in the clinician completed data forms at their site.

12.3.4 Investigator Documentation

The local Principal Investigator is responsible for maintenance of their site's Investigator Site File, including filing updates provided by the UCON Trial Office

Prior to beginning the study, each Investigator will be asked to provide particular essential documents to the BCTU, including but not limited to:

- An original signed Investigator's Declaration (as part of the Clinical Trial Agreement documents), detailing their commitment to accrual, compliance, GCP, confidentiality and publication. Deviations from the agreement will be monitored and the TSC will decide whether any action needs to be taken, e.g. withdrawal of funding, suspension of centre.
- Curriculum vitae (CV) signed and dated by the Investigator indicating that it is accurate and current.

The UCON Trial Office will ensure all other documents required by ICH GCP are retained in a Trial Master File (TMF), where required, and that appropriate documentation is available in local ISFs.

12.3.5 GCP Training

All study staff must hold evidence of appropriate GCP training.

12.3.6 Confidentiality

All endometrial biopsy samples, data collection forms and patient questionnaires must be identified in a manner designed to maintain participant confidentiality. All records must be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the participant. All investigators and study site staff involved with this study may not

disclose or use for any purpose other than performance of the study, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

All personal information received in paper format for the trial will be held securely and treated as strictly confidential according to BCTU policies. All staff involved in the UCON Trial (clinical, academic, BCTU) share the same duty of care to prevent unauthorised disclosure of personal information. No data that could be used to identify an individual will be published. Data will be stored on a secure server at Birmingham Clinical Trials Unit (BCTU) under the provisions of the Data Protection Act and/or applicable laws and regulations.

12.3.7 Data Protection

All Investigators and study site staff involved with this study must comply with the requirements of the Data Protection Act 1998 with regard to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles. Access to collated participant data will be restricted to designated staff at the UCON Trial Office, clinicians treating the participants, representatives of the sponsor(s) and representatives of regulatory authorities.

Computers used to collate the data will have limited access measures via user names and passwords.

Published results will not contain any personal data that could allow identification of individual participants.

13 STUDY CONDUCT RESPONSIBILITIES

13.1 PROTOCOL AMENDMENTS

Any changes in research activity, except those necessary to remove an apparent, immediate hazard to the participant in the case of an urgent safety measure, must be reviewed and approved by the Chief Investigator.

Amendments to the protocol must be submitted in writing to the appropriate REC, Regulatory Authority and local R&D for approval prior to participants being enrolled into an amended protocol.

13.2 PROTOCOL VIOLATIONS AND DEVIATIONS

Prospective protocol deviations, i.e. protocol waivers, will not be approved by the sponsors and therefore will not be implemented, except where necessary to eliminate an immediate hazard to study participants. If this necessitates a subsequent protocol amendment, this should be submitted to the REC, Regulatory Authority and local R&D for review and approval if appropriate.

Protocol deviations will be recorded in a protocol deviation log and logs will be submitted to the sponsors every 3 months. Each protocol violation will be reported to the sponsor within 24 hours of becoming aware of the violation.

Deviations and violations are non-compliance events discovered after the event has occurred. Deviation logs will be maintained for each site in multi-centre studies. An alternative frequency of deviation log submission to the sponsors may be agreed in writing with the sponsors.

13.3 SERIOUS BREACH REQUIREMENTS

A serious breach is a breach which is likely to effect to a significant degree:

1. the safety or physical or mental integrity of the participants of the trial; or
2. the scientific value of the trial.

If a potential serious breach is identified by the Chief investigator, Principal Investigator or delegates, the co-sponsors (accord.seriousbreach@ed.ac.uk) must be notified within 24 hours. It is the responsibility of the co-sponsors to assess the impact of the breach on the scientific value of the trial, to determine whether the incident constitutes a serious breach and report to regulatory authorities and research ethics committees as necessary. Details received by ACCORD will be passed on to BCTU in their capacity as Coordinating Centre.

13.4 STUDY RECORD RETENTION

In line with the Medicines for Human Use (Clinical Trials) Regulations, once data collection is complete on all participants, at the end of the study, all data will be stored for at least 15 years. This will allow adequate time for review and reappraisal, and form the basis for further follow-up research. Any queries or concerns about the data, conduct or conclusions of the trial can also be resolved in this time. When the minimum retention period has elapsed, study documentation will not be destroyed without permission from the sponsor.

13.5 END OF STUDY

The end of study is defined as the completion of the last participant's 12-month follow-up assessment unless PAECs are detected at this time. Should PAECs be diagnosed at 12 months then the end of study is determined by an additional biopsy(ies) and the resolution of the PAECs at either 15 or 18 months. The funder and/or Investigators and/or the trial steering committee and/or the co-sponsor(s) have the right at any time to terminate the study for clinical or administrative reasons.

The end of the study will be reported to the REC and Regulatory Authority within 90 days, or 15 days if the study is terminated prematurely. The Investigators will inform participants of the premature study closure and ensure that the appropriate follow up is arranged for all participants involved.

A summary report of the study will be provided to the REC and Regulatory Authority within 1 year of the end of the study.

13.6 CONTINUATION OF DRUG FOLLOWING THE END OF STUDY

Although UPA is a licensed drug for the treatment of uterine fibroids, it is not routinely prescribed for the treatment of heavy menstrual bleeding. Justification for the use of UPA after the trial will have to be discussed at the centre on a case-by-case basis; this discussion will be outside the remit of the trial.

13.7 INSURANCE AND INDEMNITY

The co-sponsors are responsible for ensuring proper provision has been made for insurance or indemnity to cover their liability and the liability of the Chief Investigator and staff.

The following arrangements are in place to fulfil the co-sponsors' responsibilities:

- The Protocol has been designed by the Chief Investigator and researchers employed by the University and collaborators. The University has insurance in place (which includes no-fault compensation) for negligent harm caused by poor protocol design by the Chief Investigator and researchers employed by the University.

- Sites participating in the study will be liable for clinical negligence and other negligent harm to individuals taking part in the study and covered by the duty of care owed to them by the sites concerned. The co-sponsors require individual sites participating in the study to arrange for their own insurance or indemnity in respect of these liabilities.

- Sites which are part of the United Kingdom's Nation Health Service will have the benefit of NHS Indemnity.

- The manufacturer supplying IMP has accepted limited liability related to the manufacturing and original packaging of the study drug and to the losses, damages, claims or liabilities incurred by study participants based on known or unknown Adverse Events which arise out of the manufacturing and original packaging of the study drug, but not where there is any modification to the study drug (including without limitation re-packaging and blinding).

14 REPORTING, PUBLICATIONS AND NOTIFICATION OF RESULTS

14.1 AUTHORSHIP POLICY

Ownership of the data arising from this study resides with the grant holders. On completion of the study, the study data will be analysed and tabulated, and a clinical study report will be prepared in accordance with ICH guidelines. A writing committee may be established to prepare the report.

The main report of the trial will be published in the name of the UCON Collaborative Group, acknowledging the writing group as authors. Subsequent publications should also be published in the UCON Collaborative Group name, but those academics who contribute to specific aspects may be listed as authors.

14.2 PUBLICATION

The clinical study report will be used for publication and presentation at scientific meetings. Investigators have the right to publish orally or in writing the results of the study.
A meeting will be held after the end of the study to allow discussion of the main results among the collaborators prior to publication. The success of the study depends entirely on the wholehearted collaboration of a large number of doctors, nurses and others. For this reason, chief credit for the main results will be given not to the committees or central organisers but to all those who have collaborated in the study, who will be listed as members the UCON Collaborative Group in all publications. Centres will be permitted to publish data obtained from participants in the UCON Trial that use trial outcome measures but do not relate to the trial randomised evaluation and hypothesis.

15 REFERENCES

1. Rahn DD, Abed H, Sung VW, Matteson KA, Rogers RG, Morrill MY, et al. Systematic review highlights difficulty interpreting diverse clinical outcomes in abnormal uterine bleeding trials. J Clin Epidemiol. 2011;64(3):293-300.

2. Abdel-Aleem H, d'Arcangues C, Vogelsong KM, Gulmezoglu AM. Treatment of vaginal bleeding irregularities induced by progestin only contraceptives. Cochrane Database Syst Rev. 2007(4):CD003449.

3. Gupta J, Kai J, Middleton L, Pattison H, Gray R, Daniels J. Levonorgestrel intrauterine system versus medical therapy for menorrhagia. N Engl J Med. 2013;368(2):128-37.

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

5. 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(5):591-8.

6. 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 Gynecol Pathol. 2012;31(6):556-69.

7. Pohl O, Williams AR, Bergeron C, Gotteland JP. A 39-week oral toxicity study of ulipristal acetate in cynomolgus monkeys. Regul Toxicol Pharmacol. 2013;66(1):6-12.

8. Mutter GL, Ince TA, Baak JP, Kust GA, Zhou XP, Eng C. Molecular identification of latent precancers in histologically normal endometrium. Cancer Res. 2001;61(11):4311-4.

9. Daikoku T, Hirota Y, Tranguch S, Joshi AR, DeMayo FJ, Lydon JP, et al. Conditional loss of uterine Pten unfailingly and rapidly induces endometrial cancer in mice. Cancer Res. 2008;68(14):5619-27.

10. Mutter GL, Lin MC, Fitzgerald JT, Kum JB, Baak JP, Lees JA, et al. Altered PTEN expression as a diagnostic marker for the earliest endometrial precancers. J Natl Cancer Inst. 2000;92(11):924-30.

11. Orbo A, Rise CE, Mutter GL. Regression of latent endometrial precancers by progestin infiltrated intrauterine device. Cancer Res. 2006;66(11):5613-7.

12. Zheng W, Baker HE, Mutter GL. Involution of PTEN-null endometrial glands with progestin therapy. Gynecol Oncol. 2004;92(3):1008-13.

13. Shaw RW, Brickley MR, Evans L, Edwards MJ. Perceptions of women on the impact of menorrhagia on their health using multi-attribute utility assessment. BrJObstetGynaecol. 1998;105(11):1155-9.

14. Higham JM, O'Brien PM, Shaw RW. Assessment of menstrual blood loss using a pictorial chart. Br J Obstet Gynaecol. 1990;97(8):734-9.

15. Spies JB, Coyne K, Guaou Guaou N, Boyle D, Skyrnarz-Murphy K, Gonzalves SM. The UFSQOL, a new disease-specific symptom and health-related quality of life questionnaire for leiomyomata. Obstet Gynecol. 2002;99(2):290-300.

16. Thirlaway K, Fallowfield L, Cuzick J. The Sexual Activity Questionnaire: a measure of women's sexual functioning. Qual Life Res. 1996;5(1):81-90.

17. Wilkens J, Male V, Ghazal P, Forster T, Gibson DA, Williams AR, et al. Uterine NK cells regulate endometrial bleeding in women and are suppressed by the progesterone receptor modulator asoprisnil. J Immunol. 2013;191(5):2226-35.

18. Henderson TA, Saunders PT, Moffett-King A, Groome NP, Critchley HO. Steroid receptor expression in uterine natural killer cells. J Clin Endocrinol Metab. 2003;88(1):440-9.

19. Wilkens J, Williams AR, Chwalisz K, Han C, Cameron IT, Critchley HO. Effect of asoprisnil on uterine proliferation markers and endometrial expression of the tumour suppressor gene, PTEN. Hum Reprod. 2009;24(5):1036-44.

20. Joe BN, Suh J, Hildebolt CF, Hovsepian DM, Johnston B, Bae KT. MR volumetric measurements of the myomatous uterus: improved reliability of stereology over linear measurements. Acad Radiol. 2007;14(4):455-62.

21. Gupta J, Kai J, Middleton L, Pattison H, Gray R, Daniels, J for the ECLIPSE Trial Collaborative Group. Levonorgestrel Intrauterine System versus Medical Therapy for Menorrhagia. N Engl J Med 2013; 368:128-137

22. Norman GR, Sloan JA, Wyrwich KW. Interpretation of changes in health-related quality of life: the remarkable universality of half a standard deviation. Med Care. 2003;41(5):582-92.35.

APPENDIX 1: SmPC for Esmya 5 mg Tablets (Ulipristal Acetate) – 14th January 2014

Esmya 5 mg Tablets (ulipristal acetate)

Summary of Product Characteristics Updated 14-Jan-2014 | Gedeon Richter (UK) Ltd

1. Name of the medicinal product

Esmya 5 mg tablets

2. Qualitative and quantitative composition

Each tablet contains 5 mg of ulipristal acetate.

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Tablet.

White to off-white, round biconvex tablet of 7 mm engraved with "ES5" on one face.

4. Clinical particulars

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

4.2 Posology and method of administration

Posology
The treatment consists of one tablet of 5 mg to be taken orally once daily for up to 3 months.
This 3-month treatment course can be repeated once. Re-treatment should start at the earliest during the second menstruation following the first treatment course completion.

Treatments should always be started during the first week of menstruation. Due to the lack of long term safety data, the duration of treatment should not exceed two treatment courses of 3 months.

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

Special population
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 unless the patient is closely monitored (see sections 4.4 and 5.2).

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 sections 4.4 and 5.2).

Paediatric population
There is no relevant use of ulipristal acetate in the paediatric population. The safety and efficacy of ulipristal acetate was only established in women of 18 years and older.

Method of administration
Tablets may be taken with or without food.

4.3 Contraindications
Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Pregnancy and breastfeeding.

Genital bleeding of unknown aetiology or for reasons other than uterine fibroids. Uterine, cervical, ovarian or breast cancer.

4.4 Special warnings and precautions for use
Ulipristal acetate should only be prescribed after careful diagnosis. Pregnancy should be precluded prior to treatment.

Contraception
Concomitant use of progestagen-only pills, a progestagen-releasing intrauterine device or combined oral contraceptive pills is not recommended (see sections 4.5). Although a majority of women taking a therapeutic dose of ulipristal acetate have anovulation, a non hormonal contraceptive method is recommended during treatment.

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).

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).

Concomitant treatments
Co-administration of moderate (e.g. erythromycin, grapefruit juice, verapamil) or potent (e.g. ketoconazole, ritonavir, nefazodone, itraconazole, telithromycin, clarithromycin) CYP3A4 inhibitors and ulipristal acetate is not recommended (see section 4.5).

Concomitant use of ulipristal acetate and potent CYP3A4 inducers (e.g. rifampicin, rifabutin, carbamazepine, oxcarbazepine, phenytoin, fosphenytoin, phenobarbital, primidone, St John´s wort, efavirenz, nevirapine, long term use of ritonavir) is not recommended (see section 4.5).

Asthma patients
Use in women with severe asthma insufficiently controlled by oral glucocorticoids is not recommended.

Endometrial changes
Ulipristal acetate has a specific pharmacodynamic action on the endometrium. Increase in thickness of the endometrium may occur. If the endometrial thickening persists beyond 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" (PAEC) and should not be mistaken for endometrial hyperplasia (see sections 4.8 and 5.1).

Only two treatment courses are recommended. The two treatment courses should each not exceed 3 months as the risk of adverse impact on the endometrium is unknown if treatment is continued.

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.

4.5 Interaction with other medicinal products and other forms of interaction

Potential for other medicinal products to affect ulipristal acetate:
Hormonal contraceptives
Ulipristal acetate has a steroid structure and acts as a selective progesterone receptor modulator with predominantly inhibitory effects on the progesterone receptor. Thus hormonal contraceptives and progestagens are likely to reduce ulipristal acetate efficacy by competitive action on the progesterone receptor. Therefore concomitant administration of medicinal products containing progestagen is not recommended (see section 4.4 and 4.6).

CYP3A4 inhibitors
Following administration of the moderate CYP3A4 inhibitor erythromycin propionate (500 mg twice daily for 9 days) to healthy female volunteers, C_{max} and AUC of ulipristal acetate increased 1.2 and 2.9 fold, respectively; the AUC of the active metabolite of ulipristal acetate increased 1.5 fold while the C_{max} of the active metabolite decreased (0.52 fold change).

Following administration of the potent CYP3A4 inhibitor ketoconazole (400 mg once daily for 7 days) to healthy female volunteers, C_{max} and AUC of ulipristal acetate increased 2 and 5.9 fold, respectively; the AUC of the active metabolite of ulipristal acetate increased 2.4 fold while the C_{max} of the active metabolite decreased (0.53 fold change).

No dose adjustment is considered necessary for administration of ulipristal acetate to patients receiving concomitant mild CYP3A4 inhibitors. Co-administration of moderate or potent CYP3A4 inhibitors and ulipristal acetate is not recommended (see section 4.4).

CYP3A4 inducers

Administration of the potent CYP3A4 inducer rifampicin (300 mg twice daily for 9 days) to healthy female volunteers markedly decreased C_{max} and AUC of ulipristal acetate and its active metabolite by 90 % or more and decreased ulipristal acetate half-life by 2.2-fold corresponding to an approximately 10-fold decrease of ulipristal acetate exposure. Concomitant use of ulipristal acetate and potent CYP3A4 inducers (e.g. rifampicin, rifabutin, carbamazepine, oxcarbazepine, phenytoin, fosphenytoin, phenobarbital, primidone, St John´s wort, efavirenz, nevirapine, long term use of ritonavir) is not recommended (see section 4.4).

Medicinal products affecting gastric pH

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 C_{max}, a delayed t_{max} (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.

<u>Potential for ulipristal acetate to affect other medicinal products:</u>

Hormonal contraceptives

Ulipristal acetate may interfere with the action of hormonal contraceptive products (progestagen only, progestagen releasing devices or combined oral contraceptive pills) and progestagen administered for other reasons. Therefore concomitant administration of medicinal products containing progestagen is not recommended (see sections 4.4 and 4.6). Medicinal products containing progestagen should not be taken within 12 days after cessation of ulipristal acetate treatment.

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.

Simultaneous administration of ulipristal acetate and a P-gp substrate has not been studied and an interaction cannot be excluded. *In vivo* results show that ulipristal acetate (administered as a single 10 mg tablet) 1.5 hour before administration of the P-gP substrate fexofenadine (60 mg) has no clinically relevant effects on the pharmacokinetic of fexofenadine. It is therefore recommended that co-administration of ulipristal acetate and P-gp substrates (e.g. dabigatran etexilate, digoxin, fexofenadine) should be separated in time by at least 1.5 hours.

4.6 Fertility, pregnancy and lactation

<u>Contraception in females</u>

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 ulipristal acetate have anovulation, a non hormonal contraceptive method is recommended during treatment (see sections 4.4 and 4.5).

<u>Pregnancy</u>

Ulipristal acetate is contraindicated during pregnancy (see section 4.3).

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 (see section 5.3).

Breast-feeding
Available toxicological data in animals have shown excretion of ulipristal acetate in milk (for details see section 5.3). Ulipristal acetate is excreted in human milk. The effect on newborn/infants has not been studied. A risk to the newborns/infants cannot be excluded. Ulipristal acetate is contraindicated during breast-feeding (see sections 4.3 and 5.2).

Fertility
A majority of women taking a therapeutic dose of ulipristal acetate have anovulation, however, the level of fertility while taking multiple doses of ulipristal acetate has not been studied.

4.7 Effects on ability to drive and use machines
Ulipristal acetate may have minor influence on the ability to drive or use machines as mild dizziness has been observed after ulipristal acetate intake.

4.8 Undesirable effects
Summary of the safety profile
The safety of ulipristal acetate has been evaluated in 602 women with uterine fibroids treated with 5 mg or 10 mg ulipristal acetate during Phase III studies. The most common finding in clinical trials was amenorrhea (80.8%), which is considered as a desirable outcome for the patients (see section 4.4).
The most frequent adverse reaction was hot flush. The vast majority of adverse reactions were mild and moderate (93.6%), did not lead to discontinuation of the medicinal product (99.5%) and resolved spontaneously.

The safety of two intermittent treatment courses (each limited to 3 months) has been evaluated in 131 women with uterine fibroids treated with 10 mg ulipristal acetate in a phase III study and demonstrated a similar safety profile to that observed for one treatment course.

Tabulated list of adverse reactions
Based on pooled data from three phase III studies in patients with uterine fibroids treated for 3 months, the following adverse reactions have been reported. Adverse reactions listed below are classified according to frequency and system organ class. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. Frequencies are defined as very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000) and not known (cannot be estimated from available data).

System Organ Class	Adverse reactions		
	Very common	**Common**	**Uncommon**
Psychiatric disorders			Anxiety Emotional disorder
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	Alopecia** Dry skin
Musculoskeletal and connective tissue disorders		Musculoskeletal pain	Back pain
Renal and urinary disorders			Urinary incontinence
Reproductive system and breast disorders	Amenorrhea Endometrial thickening*	Uterine haemorrhage* Hot flush* Pelvic pain Ovarian cyst* Breast tenderness/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

* see section "Description of selected adverse reactions"
** The verbatim term “mild hair loss” was coded to the term “alopecia”

Description of selected adverse reactions

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.

In addition, reversible changes to the endometrium are denoted PAEC and are different from endometrial hyperplasia. If hysterectomy or endometrial biopsy specimens are sent for histology, then the pathologist should be informed that the patient has taken ulipristal acetate (see sections 4.4 and 5.1).

Hot flush

Hot flushes were reported by 9.8% 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. In the open-label phase III clinical trial, the frequency was 4.3% for ulipristal acetate.

Headache
Mild or moderate severity headache was reported in 6.8% of patients.

Ovarian cyst
Functional ovarian cysts were observed during and after treatment in 1.2% of patients and in most of the cases spontaneously disappeared within a few weeks.

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.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the MHRA Yellow Card Scheme (www.mhra.gov.uk/yellowcard)

4.9 Overdose
Experience with ulipristal acetate overdose is limited.
Single doses up to 200 mg and daily doses of 50 mg for 10 consecutive days were administered to a limited number of subjects, and no severe or serious adverse reactions were reported.

5. Pharmacological properties

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Sex hormones and modulators of the genital system, progesterone receptor modulators. ATC code: G03XB02.

Ulipristal acetate is an orally-active synthetic selective progesterone receptor modulator characterised by a tissue-specific partial progesterone antagonist effect.

Endometrium
Ulipristal acetate exerts a direct effect on the endometrium. When daily administration of a 5 mg dose is commenced during a menstrual cycle most subjects (including patients with myoma) will complete their first menstruation but will not menstruate again until after treatment is stopped. When ulipristal acetate treatment is stopped, menstrual cycles generally resume within 4 weeks.

The direct action on the endometrium results in class-specific changes in histology termed PAEC. Typically, the histological appearance is an inactive and weakly proliferating 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.

About 5% of patients of reproductive age experiencing heavy menstrual bleeding have an endometrial thickness of greater than 16 mm. 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 endometrial thickness persists beyond 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.

Fibroids

Ulipristal acetate exerts a direct action on fibroids reducing their size through inhibition of cell proliferation and induction of apoptosis.

Pituitary

A daily dose of ulipristal acetate 5 mg inhibits ovulation in the majority of patients as indicated by progesterone levels maintained at around 0.3 ng/ml.

A daily dose of ulipristal acetate 5 mg partially suppresses FSH levels but serum oestradiol levels are maintained in the mid-follicular range in the majority of patients and are similar to levels in patients who received placebo.

Ulipristal acetate does not affect serum levels of TSH, ACTH or prolactin during 3 months of treatment.

Clinical efficacy and safety

The efficacy of fixed doses of ulipristal acetate 5 mg and 10 mg once daily was evaluated in two Phase 3 randomised, double-blind, 13 week studies recruiting patients with very heavy menstrual bleeding associated with uterine fibroids. Study 1 was double-blind placebo controlled. Patients in this study were required to be anaemic at Study entry (Hb < 10.2 g/dl) and all patients were to receive oral iron 80 mg Fe++ in addition to study drug. Study 2 contained the active comparator, leuprorelin 3.75 mg given once per month by intramuscular injection. In Study 2, a double-dummy method was used to maintain the blind. In both studies menstrual blood loss was assessed using the Pictorial Bleeding Assessment Chart (PBAC). A PBAC >100 within the first 8 days of menses is considered to represent excessive menstrual blood loss.

In study 1, a statistically significant difference was observed in reduction in menstrual blood loss in favour of the patients treated with ulipristal acetate compared to placebo (see Table 1 below), resulting in faster and more efficient correction of anaemia than iron alone. Likewise, patients treated with ulipristal acetate had a greater reduction in myoma size, as assessed by MRI.

In study 2, the reduction in menstrual blood loss was comparable for the patients treated with ulipristal acetate and the gonadotrophin releasing hormone-agonist (leuprorelin). Most patients treated with ulipristal acetate stopped bleeding within the first week of treatment (amenorrhea).
The size of the three largest myomas was assessed by ultrasound at the end of treatment (Week 13) and for another 25 weeks without treatment in patients who did not have hysterectomy or myomectomy performed. Myoma size reduction was generally maintained during this follow-up period in patients originally treated with ulipristal acetate but some re-growth occurred in patients treated with leuprorelin.

Table 1: Results of primary and selected secondary efficacy assessments in Phase III studies

Parameter	Study 1			Study 2		
	Placebo **N = 48**	**Ulipristal acetate 5 mg/day** **N = 95**	**Ulipristal acetate 10 mg/day** **N = 94**	**Leuprorelin 3.75 mg/ month** **N = 93**	**Ulipristal acetate 5 mg/day** **N = 93**	**Ulipristal acetate 10 mg/day** **N = 95**
Menstrual bleeding						
Median PBAC at baseline	376	386	330	297	286	271
Median change at week 13	-59	**-329**	**-326**	-274	-268	-268
Patients in **amenorrhea** at week 13	3 (6.3%)	**69 (73.4%)**[1]	**76 (81.7%)**[2]	74 (80.4%)	70 (75.3%)	85 (89.5%)
Patients whose menstrual bleeding became normal (PBAC < 75) at week 13	9 (18.8%)	**86 (91.5%)**[1]	**86 (92.5%)**[1]	82 (89.1%)	84 (90.3%)	93 (97.9%)
Median change in **myoma volume** from baseline to week 13[a]	+3.0%	**-21.2%**[3]	**-12.3%**[4]	-53.5%	-35.6%	-42.1%

[a] In Study 1, change from baseline in total myoma volume was measured by MRI. In Study 2, change in the volume of the three largest myomas was measured by ultrasound. Bold values in shaded squares indicate that there was a significant difference in the comparisons between ulipristal acetate and the control. These were always in favour of ulipristal acetate.

P values: [1] = <0.001, [2] = 0.037, [3]= <0.002, [4] = <0.006.

In a phase III study in 131 women with uterine fibroids receiving two intermittent 3-month treatment courses of ulipristal acetate 10 mg, amenorrhea was achieved at the end of the first treatment course in 79.5% of subjects. The second treatment course provided comparable results (88.5% of subjects). Myoma volume reduction (mean [median] change from screening) observed during the first treatment course (-41.9% [-49.9%]) was maintained during the second one (-43.7% [-63.2%]). In view of studies 1 and 2 results, it is expected that similarly to the 10 mg dose the efficacy of the 5 mg dose in the first treatment course will be maintained in the second treatment course.

Although the number of patients that completed the four treatment courses of 3 months is limited, i.e. 99 patients, the safety data are sufficient to support one additional 3-month treatment course in a pre-operative setting.

The European Medicines Agency has waived the obligation to submit the results of studies with Esmya in all subsets of the paediatric population in leiomyoma of uterus (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

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 acetate tablets.

Distribution

Ulipristal acetate is highly bound (>98%) to plasma proteins, including albumin, alpha-l-acid glycoprotein, high density lipoprotein and low density lipoprotein.
Ulipristal acetate and its active mono-N-demethylated metabolite are excreted in breast milk with a mean AUCt milk/plasma ratio of 0.74 ± 0.32 for ulipristal acetate.

Biotransformation/Elimination

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.

Special populations

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 (see sections 4.2 and 4.4).

5.3 Preclinical safety data

Non-clinical data 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. In a 39 week study in cynomolgus monkeys, histological changes resembling PAEC were noted at low doses.

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.

Carcinogenicity studies (in rats and mice) showed that ulipristal acetate is not carcinogenic.

6. Pharmaceutical particulars
6.1 List of excipients
Microcrystalline cellulose
Mannitol
Croscarmellose sodium
Talc
Magnesium stearate

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
3 years.

6.4 Special precautions for storage
Keep the blisters in the outer carton in order to protect from light.

6.5 Nature and contents of container
Alu-PVC/PE/PVDC blister.
Pack of 28 and 84 tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling
No special requirements.

7. Marketing authorisation holder
Gedeon Richter Plc.
Gyömrői út 19-21.
1103 Budapest
Hungary
8. Marketing authorisation number(s)
EU/1/12/750/001
EU/1/12/750/002

9. Date of first authorisation/renewal of the authorisation
Date of first authorisation: 23 February 2012

10. Date of revision of the text
18 December 2013

Detailed information on this product is available on the website of the European Medicines Agency http://www.ema.europa.eu

Company Contact Details
Gedeon Richter (UK) Ltd
http://www.preglem.com

Address
Women's Health Division, 127 Shirland Road, London, W9 2EP

Fax
Medical Information e-mail
medinfo.uk@gedeonrichter.eu

Medical Information Fax
Telephone
+44(0)207 604 8800

Medical Information Direct Line
+44 (0)207 604 8806

Customer Care direct line
+44 (0)207 604 8800

APPENDIX 2: SmPC for LNG-IUS (Mirena) - Updated 11th June 2013

Mirena

Summary of Product Characteristics Updated 11-Jun-2013 | Bayer plc

1. Name of the medicinal product

Mirena® 20 micrograms/24 hours intrauterine delivery system

2. Qualitative and quantitative composition

Levonorgestrel 52mg.

The initial release of levonorgestrel is approximately 20 micrograms per day reducing to approximately 10 micrograms per day after 5 years in women using Mirena for contraception or treatment of menorrhagia. It is estimated, by extrapolation from pre-menopausal women, that the release of levonorgestrel is approximately 12 micrograms per day after 4 years in women using Mirena as part of hormone replacement therapy.

For a full list of excipients, see section 6.1

3. Pharmaceutical form

Levonorgestrel-releasing intrauterine system (IUS).

The product consists of an inserter and levonorgestrel intrauterine system, which is loaded at the tip of the inserter. Inserter components are an insertion tube, plunger, flange, body and slider. The system consists of a white or almost white hormone-elastomer core, mounted on a T-body and covered in opaque tubing, which regulates the release of levonorgestrel. The T-body has a loop at one end and two arms at the other end. Removal threads are attached to the loop.

4. Clinical particulars

4.1 Therapeutic indications

Contraception.

Idiopathic menorrhagia. Mirena may be particularly useful in women with idiopathic menorrhagia requiring (reversible) contraception.

Protection from endometrial hyperplasia during oestrogen replacement therapy.

4.2 Posology and method of administration

Starting treatment

• Contraception and idiopathic menorrhagia

In women of fertile age, Mirena is inserted into the uterine cavity within seven days of the onset of menstruation. It can be replaced by a new system at any time of the cycle.

Post-partum insertion: To reduce the risk of perforation, postpartum insertions should be postponed until the uterus is fully involuted. Do not insert earlier than six weeks after delivery. If the patient is experiencing significant post-partum bleeding and/or pain then infection or other causes should be excluded before insertion. Mirena can also be inserted immediately after the first trimester abortion.

Mirena is effective for 5 years in the indications for contraception and idiopathic menorrhagia so should be removed after 5 years use. If the user wishes to continue using the same method, a new system can be inserted at the same time, in which case no additional protection is required.

If pregnancy is not desired, the removal should be carried out during the first few days after the onset of the woman's menstruation. Otherwise contraception has to be ensured with other methods (e.g. condoms) starting at least 7 days before the removal.

• Protection from endometrial hyperplasia during oestrogen replacement therapy.

When used for endometrial protection during oestrogen replacement therapy, Mirena can be inserted at any time in an amenorrhoeic woman, or during the last days of menstruation or withdrawal bleeding.

In the indication for protection from endometrial hyperplasia during oestrogen replacement therapy, clinical data (from clinical trials conducted in women of 18 years and over) beyond 4 years of use are limited. Mirena should therefore be removed after 4 years.

Mirena provides the progestogen component of hormone therapy (HRT). Therefore in women receiving HRT, Mirena can be used in combination with oral or transdermal oestrogen preparations without additional exogenous progestogens. The product information of the oestrogen component of the HRT should be consulted prior to the use of Mirena as the important risk factors associated with HRT use should be considered, such as the risk of endometrial cancer, breast cancer and venous thromboembolisms.

Instructions for use and handling

Only to be inserted by a trained healthcare professional using aseptic technique.

Mirena is supplied within an inserter in a sterile package which should not be opened until needed for insertion. The exposed product should be handled with aseptic precautions. If the seal of the sterile package is broken, the product should be discarded (see Section 6.6 for disposal instructions).

How to Insert Mirena

It is strongly recommended that Mirena should only be inserted by physicians/healthcare professionals who are experienced in Mirena insertions and/or have undergone sufficient training for Mirena insertion.

In case of difficult insertion and/or exceptional pain or bleeding during or after insertion, please refer to section 4.4.

• Mirena is supplied sterile having been sterilised with ethylene oxide. Do not resterilise. For single use only. Do not use if the inner package is damaged or open. Insert before the month and year shown on the label.

• Mirena is inserted with the provided inserter (figure 1) into the uterine cavity by carefully following the insertion instructions.

Preparation for insertion

• Examine the patient to establish the size and position of the uterus, in order to detect any signs of acute genital infections or other contraindications for the insertion of Mirena and to exclude pregnancy.

• Insert a speculum, visualise the cervix and then thoroughly cleanse the cervix and vagina with a suitable antiseptic solution.

• Use an assistant as necessary.

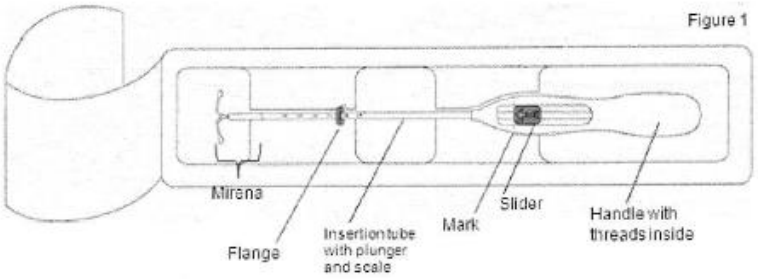
• Grasp the anterior lip of the cervix with a tenaculum or other forceps to stabilise the uterus. If the uterus is retroverted, it may be more appropriate to grasp the posterior lip of the cervix. Gentle traction on the forceps can be applied to straighten the cervical canal. The forceps should remain in position and gentle counter traction on the cervix should be maintained throughout the insertion procedure.

• Advance a uterine sound through the cervical canal to the fundus to measure the depth and confirm the direction of the uterine cavity and to exclude any evidence of intrauterine abnormalities (e.g. septum, submucous fibroids) or a previously inserted intrauterine contraceptive which has not been removed. If difficulty is encountered, consider dilatation of the canal. If cervical dilatation is required, consider using analgesics and/or a paracervical block.

Insertion

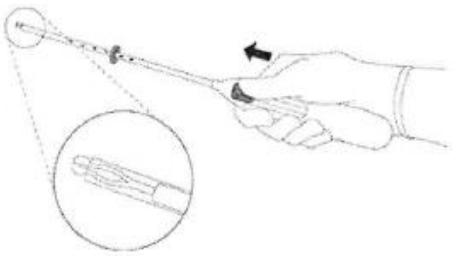
1. First, open the sterile package completely (Figure 1). Then use sterile technique and sterile gloves.

Figure 1



2. Push the slider **forward** in the direction of the arrow to the furthest position to load Mirena into the insertion tube (Figure 2).

Figure 2



IMPORTANT! Do not pull the slider downwards as this may prematurely release Mirena. Once released, Mirena cannot be re-loaded.

3. Holding the slider in the furthest position,

Only to be inserted by a trained healthcare professional using aseptic technique.

Mirena is supplied within an inserter in a sterile package which should not be opened until needed for insertion. The exposed product should be handled with aseptic precautions. If the seal of the sterile package is broken, the product should be discarded (see Section 6.6 for disposal instructions).

How to Insert Mirena

It is strongly recommended that Mirena should only be inserted by physicians/healthcare professionals who are experienced in Mirena insertions and/or have undergone sufficient training for Mirena insertion.

In case of difficult insertion and/or exceptional pain or bleeding during or after insertion, please refer to section 4.4.

• Mirena is supplied sterile having been sterilised with ethylene oxide. Do not resterilise. For single use only. Do not use if the inner package is damaged or open. Insert before the month and year shown on the label.

• Mirena is inserted with the provided inserter (figure 1) into the uterine cavity by carefully following the insertion instructions.

Preparation for insertion

• Examine the patient to establish the size and position of the uterus, in order to detect any signs of acute genital infections or other contraindications for the insertion of Mirena and to exclude pregnancy.

• Insert a speculum, visualise the cervix and then thoroughly cleanse the cervix and vagina with a suitable antiseptic solution.

• Use an assistant as necessary.

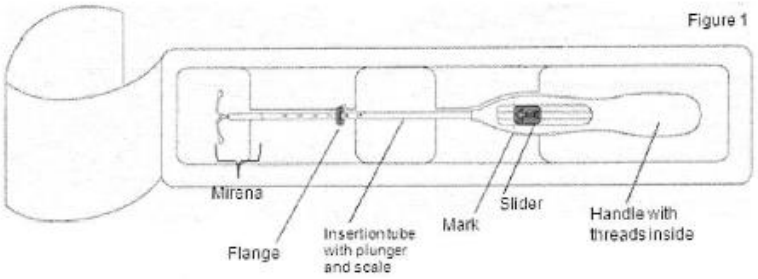
• Grasp the anterior lip of the cervix with a tenaculum or other forceps to stabilise the uterus. If the uterus is retroverted, it may be more appropriate to grasp the posterior lip of the cervix. Gentle traction on the forceps can be applied to straighten the cervical canal. The forceps should remain in position and gentle counter traction on the cervix should be maintained throughout the insertion procedure.

• Advance a uterine sound through the cervical canal to the fundus to measure the depth and confirm the direction of the uterine cavity and to exclude any evidence of intrauterine abnormalities (e.g. septum, submucous fibroids) or a previously inserted intrauterine contraceptive which has not been removed. If difficulty is encountered, consider dilatation of the canal. If cervical dilatation is required, consider using analgesics and/or a paracervical block.

Insertion

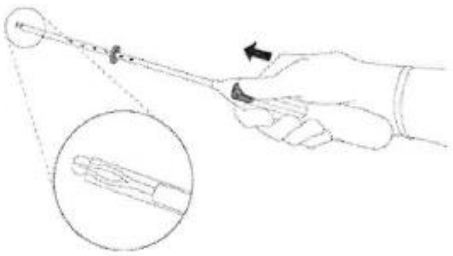
1. First, open the sterile package completely (Figure 1). Then use sterile technique and sterile gloves.

Figure 1



2. Push the slider **forward** in the direction of the arrow to the furthest position to load Mirena into the insertion tube (Figure 2).

Figure 2

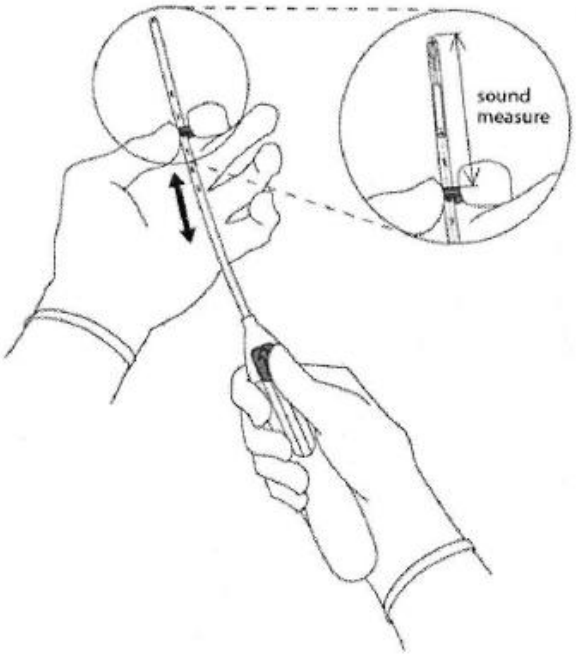


IMPORTANT! Do not pull the slider downwards as this may prematurely release Mirena. Once released, Mirena cannot be re-loaded.

3. Holding the slider in the furthest position,

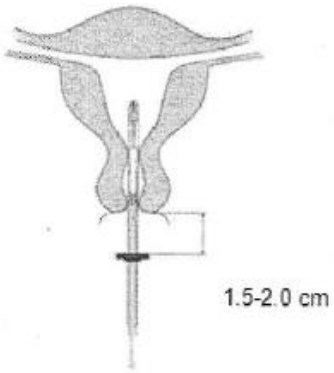
set the **upper** edge of the flange to correspond to the sound measurement of the uterine depth (Figure 3).

Figure 3



4. While holding the slider in the **furthest** position, advance the inserter through the cervix until the flange is approx. 1.5-2.0 cm from the uterine cervix (Figure 4).

Figure 4



IMPORTANT! Do not force the inserter. Dilate the cervical canal, if necessary.

5. While holding the inserter steady, **pull the slider to the mark** to open the horizontal arms of Mirena (Figure 5). Wait 5-10 seconds for the horizontal arms to open completely.

IMPORTANT! Should you suspect that the system is not in the correct position, check placement (e.g. with ultrasound). Remove the system if it is not positioned properly within the uterine cavity. A removed system must not be re-inserted.

Removal/ replacement

Mirena is removed by pulling on the threads with a forceps (Figure 8).

You may insert a new Mirena immediately following removal.

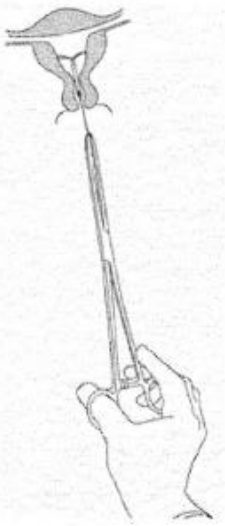


Figure 8

Mirena is removed by gently pulling on the threads with forceps. If the threads are not visible and the system is in the uterine cavity, it may be removed using a narrow tenaculum. This may require dilatation of the cervical canal or other surgical intervention.

After removal of Mirena, the system should be checked to ensure it is intact. During difficult removals, single cases have been reported of the hormone cylinder sliding over the horizontal arms and hiding them inside the cylinder. This situation does not require further intervention once completeness of the IUS has been ascertained. The knobs of the horizontal arms usually prevent complete detachment of the cylinder from the T-body.

Information on special populations

Paediatric population

There are no relevant indications for use of Mirena before menarche.

Geriatric patients

Mirena has not been studied in women over the age of 65 years.

Patients with hepatic impairment

Mirena is contraindicated in women with acute liver disease or liver tumour (see 4.3 Contraindications).

Patients with renal impairment

Mirena has not been studied in women with renal impairment.

4.3 Contraindications

- Known or suspected pregnancy
- Confirmed or suspected hormone dependent tumours including breast cancer
- Current or recurrent pelvic inflammatory disease
- Cervicitis
- Current genital infection
- Postpartum endometritis, infected abortion during the past three months
- Conditions associated with increased susceptibility to infections
- Cervical dysplasia
- Uterine or cervical malignancy

- Undiagnosed abnormal genital bleeding
- Congenital or acquired abnormality of the uterus including fibroids if they distort the uterine cavity
- Liver tumour or other acute or severe liver disease
- Acute malignancies affecting the blood or leukaemias except when in remission
- Recent trophoblastic disease while hCG levels remain elevated
- Hypersensitivity to the active substance or to any of the excipients.

Active or previous severe arterial disease, such as stroke or myocardial infarction is a contraindication when Mirena is used in conjunction with an oestrogen for HRT use.

4.4 Special warnings and precautions for use

Medical Examination

Before insertion, a complete personal and family medical history should be taken. Physical examination should be guided by this and by the contraindications and warnings for use. Pulse and blood pressure should be measured and a bimanual pelvic examination performed to establish the orientation of the uterus. The patient should be re-examined six weeks after insertion and further examinations should be performed where clinically indicated and adapted to the individual woman rather than as routine procedure. Prior to insertion pregnancy should be excluded and genital infection should be successfully treated. Women should be advised that Mirena does not protect against HIV (AIDs) and other sexually transmitted disease (please refer to the section below on pelvic infections).

Women should be encouraged to attend cervical and breast screening as appropriate for their age.

For the treatment of postmenopausal symptoms, HRT should only be initiated for symptoms that adversely affect quality of life. In all cases, a careful appraisal of the risks and benefits should be undertaken at least annually and HRT should only be continued as long as the benefit outweighs the risk. The contraindications and warnings for the oestrogen component should also be considered prior to commencing the HRT regimen.

Conditions under which Mirena can be used with caution

Should any of the following conditions exist or arise for the first time during treatment, removal of the system should be considered:

- Migraine with aura
- Unusually severe or unusually frequent headache
- Jaundice
- Marked increase of blood pressure
- Malignancies affecting the blood or leukaemias in remission
- Use of chronic corticosteroid therapy
- Past history of symptomatic functional ovarian cysts
- Active or previous severe arterial disease, such as stroke or myocardial infarction (See section 4.3 when Mirena is used in conjunction with an oestrogen for HRT use).
- Severe or multiple risk factors for arterial disease
- Thrombotic arterial or any current embolic disease
- Acute venous thromboembolism

In general, women using hormonal contraception should be encouraged to give up smoking.

Mirena should be used with caution in postmenopausal women with advanced uterine atrophy.

Insertion/removal warnings and precautions

General Information: As the insertion technique is different from other intrauterine devices, special emphasis should be given to training in the correct insertion technique. Instructions for insertion are in the package.

Insertion and removal may be associated with some pain and bleeding. In case of difficult insertion and/or exceptional pain or bleeding during or after insertion, physical examination and ultrasound should be performed immediately to exclude perforation of the uterine corpus or cervix (see also '*Perforation*').

The procedure may precipitate fainting as a vasovagal reaction, or a seizure in an epileptic patient. In the event of early signs of a vasovagal attack, insertion may need to be abandoned or the system removed. The woman should be kept supine, the head lowered and the legs elevated to the vertical position if necessary in order to restore cerebral blood flow. A clear airway must be maintained; an airway should always be at hand. Persistent bradycardia may be controlled with intravenous atropine. If oxygen is available it may be administered.

Perforation: Perforation of the uterine corpus or cervix may occur, most commonly during insertion. This may be associated with severe pain and continued bleeding. If perforation is suspected the system should be removed as soon as possible. The risk of perforation is increased in breastfeeding women and may be increased in post-partum insertions (see section 4.2) and in women with a fixed retroverted uterus.

Pelvic infection: The insertion tube helps to prevent Mirena from contamination with micro-organisms during the insertion and the Mirena inserter has been designed to minimise the risk of infections. In users of copper intrauterine devices (IUDs), the highest rate of pelvic infections occurs during the first month after insertion and decreases later.

Known risk factors for pelvic inflammatory disease are multiple sexual partners, frequent intercourse and young age. Pelvic infection may have serious consequences as it may impair fertility and increase the risk of ectopic pregnancy.

As with other gynaecological or surgical procedures, severe infection or sepsis (including group A streptococcal sepsis) can occur following IUS insertion, although this is extremely rare.

For women using Mirena with symptoms and signs suggestive of pelvic infection, bacteriological examinations are indicated and monitoring is recommended, even with discrete symptoms, and appropriate antibiotics should be started. There is no need to remove Mirena unless the symptoms fail to resolve within the following 72 hours or unless the woman wishes Mirena to be removed. Mirena must be removed if the woman experiences recurrent endometritis or pelvic infection, or if an acute infection is severe.

Complications leading to failure

Expulsion: Symptoms of the partial or complete expulsion of any IUS may include bleeding or pain. However, a system can be expelled from the uterine cavity without the woman noticing it. Partial expulsion may decrease the effectiveness of Mirena. As the system decreases menstrual flow, increase of menstrual flow may be indicative of an expulsion. A displaced Mirena should be removed and a new system inserted. The woman should be advised how to check the threads of Mirena.

Lost threads: If the retrieval threads are not visible at the cervix on follow-up examination - first exclude pregnancy. The threads may have been drawn up into the uterus or cervical canal and may reappear during the next menstrual period. If they cannot be found, they may have broken off, the system may have been expelled, or rarely the device may be extrauterine after having perforated the uterus. An ultrasound should be arranged to locate the device and alternative contraception should be advised in the mean time. If an ultrasound cannot locate the device and there is no evidence of expulsion, a plain abdominal X-ray should be performed to exclude an extrauterine device.

Bleeding irregularities

Irregular bleeding: Mirena usually achieves a significant reduction in menstrual blood loss in 3 to 6 months of treatment. Increased menstrual flow or unexpected bleeding may be indicative of expulsion. If menorrhagia persists then the woman should be re-examined. An assessment of the uterine cavity should be performed using ultrasound scan. An endometrial biopsy should also be considered.

Risk in pre-menopausal women

Because irregular bleeding/spotting may occur during the first months of therapy in pre-menopausal women, it is recommended to exclude endometrial pathology before insertion of Mirena.

Risk in post-menopausal women

If the woman continues the use of Mirena inserted earlier for contraception, endometrial pathology has to be excluded if bleeding disturbances appear after commencing oestrogen replacement therapy. If bleeding irregularities develop during a prolonged treatment, appropriate diagnostic measures should also be taken as irregular bleeding may mask symptoms and signs of endometrial polyps or cancer.

When to check for pregnancy in women of child bearing potential: The possibility of pregnancy should be considered if menstruation does not occur within six weeks of the onset of previous menstruation and expulsion should be excluded. A repeated pregnancy test is not necessary in amenorrhoeic subjects unless indicated by other symptoms. In a study in women who used Mirena for contraception (n=130), oligomenorrhoea and amenorrhoea were reported in 57% and 16% of women respectively at the end of the first year of use.

Treatment review advice for Menorrhagia: Mirena usually achieves a significant reduction in menstrual blood loss in 3 to 6 months of treatment. If significant reduction in blood loss is not achieved in these time-frames, alternative treatments should be considered.

Other risks during use

Ectopic pregnancy: The absolute risk of ectopic pregnancy in Mirena users is low. However, when a woman becomes pregnant with Mirena in situ, the relative likelihood of ectopic pregnancy is increased. The possibility of ectopic pregnancy should be considered in the case of lower abdominal pain - especially in connection with missed periods or if an amenorrhoeic woman starts bleeding. The absolute rate of ectopic pregnancy in users of Mirena is approximately 0.1% per year. This rate is lower than the rate of 0.3-0.5 % per year estimated for women not using any contraception. Women with a previous history of ectopic pregnancy carry a higher risk of a further ectopic pregnancy.

Ovarian Cysts: Since the contraceptive effect of Mirena is mainly due to its local effect, ovulatory cycles with follicular rupture usually occur in women of fertile age. Sometimes atresia of the follicle is delayed and folliculogenesis may continue. These enlarged follicles cannot be distinguished clinically from ovarian cysts. Data from clinical trials suggest that ovarian cysts have been reported as an adverse drug reaction in approximately 7% of women using Mirena, however some published studies have reported a higher incidence of ovarian cysts (which could have been influenced by factors including frequency and criteria of ultrasound scanning, and patient population). Most of these follicles are asymptomatic, although some may be accompanied by pelvic pain or dyspareunia.

In most cases, the ovarian cysts disappear spontaneously during two to three months' observation. Should this not happen, continued ultrasound monitoring and other diagnostic/therapeutic measures are recommended. Rarely, surgical intervention may be required.

Breast cancer:

Risk in pre-menopausal women

A meta-analysis from 54 epidemiological studies reported that there is a slightly increased relative risk (RR = 1.24) of having breast cancer diagnosed in women who are currently using combined oral contraceptives (COCs), mainly using oestrogen-progestogen preparations. The excess risk gradually disappears during the course of the 10 years after cessation of COC use. Because breast cancer is rare in women under 40 years of age, the excess number of breast cancer diagnoses in current and recent COC users is small in relation to the overall risk of breast cancer.

The risk of having breast cancer diagnosed in users of progestogen-only methods (POPs, implants and injectables), including Mirena, is possibly of similar magnitude to that associated with COC. However, for progestogen-only contraceptive preparations, the evidence is based on much smaller populations of users and so is less conclusive than that for COCs.

Risk in post-menopausal women

The risk of breast cancer is increased in post-menopausal women using systemic (i.e. oral or transdermal) hormone replacement therapy (HRT). This risk is higher with combined oestrogen-progestogen HRT than with oestrogen-only HRT. The risk of breast cancer when Mirena is prescribed to provide the progestogen component of HRT is not yet known. The product information of the oestrogen component of the treatment should also be consulted for additional information.

General Information

Glucose tolerance: Low-dose levonorgestrel may affect glucose tolerance, and the blood glucose concentration should be monitored in diabetic users of Mirena.

Post-coital contraception: Limited experience suggests that Mirena is not suitable for use as a post-coital contraceptive.

4.5 Interaction with other medicinal products and other forms of interaction

The metabolism of progestogens may be increased by concomitant use of substances known to induce drug-metabolising enzymes, specifically cytochrome P450 enzymes, such as anticonvulsants (e.g. phenobarbital, primidone, phenytoin, carbamazepine) and anti-infectives (e.g. griseofulvin, rifampicin, rifabutin, nevirapine, efavirenz). The influence of these drugs on the contraceptive efficacy of Mirena has not been studied but is not believed to be of major importance due to the local mechanism of action.

4.6 Fertility, pregnancy and lactation

Pregnancy: The use of Mirena during an existing or suspected pregnancy is contraindicated (see section 4.3). In case of an accidental pregnancy with Mirena in situ, ectopic pregnancy should be excluded (see section 4.4) and the system must be removed and termination of the pregnancy should be considered. Removal of Mirena or probing of the uterus may result in spontaneous abortion. Should these procedures not be possible, the woman should be informed about increased risk of spontaneous abortion or premature labour observed during the use of copper and plastic IUDs. Accordingly, such pregnancies should be closely monitored. The woman should be instructed to report all symptoms that suggest complications of the pregnancy, like cramping abdominal pain with fever.

Because of the intrauterine administration and the local exposure to the hormone, teratogenicity (especially virilisation) cannot be completely excluded. It can be expected that the systemic hormone exposure of the foetus through the maternal circulation is lower than with any other hormonal contraceptive method. Clinical experience of the outcomes of pregnancies with Mirena in situ is limited. However, the woman should be informed that, to date, there is no evidence of birth defects caused by Mirena use in cases where pregnancy continues to term with Mirena in place.

Lactation: Levonorgestrel has been identified in the breast milk. About 0.1% of the levonorgestrel dose is transferred during breast-feeding, but it is not likely that there will be a risk for the child with the dose released from Mirena, when it is inserted in the uterine cavity.

There appear to be no deleterious effects on infant growth or development when using any progestogen-only method after six weeks postpartum. Progestogen-only methods do not appear to affect the quantity or quality of breast milk. Uterine bleeding has rarely been reported in women using Mirena during lactation.

Fertility: Studies have suggested that in women who discontinue Mirena for planned pregnancy the pregnancy rate at one year is similar to those who do not use contraception.

4.7 Effects on ability to drive and use machines

There are no known effects on the ability to drive or use machines.

4.8 Undesirable effects

Undesirable effects are more common during the first months after the insertion, and subside during prolonged use.

Very common undesirable effects (occurring in more than 10% of users) include uterine/vaginal bleeding including spotting, oligomenorrhoea, amenorrhoea (see section 5.1).

The frequency of benign ovarian cysts depends on the diagnostic method used (see section 4.4) but has been estimated from clinical trial data to occur in 7% of users.

System Organ Class	Common ≥ 1/100 to < 1/10	Uncommon ≥ 1/1000 to < 1/100	Rare ≥ 1/10,000 to < 1/1000	Unknown
Immune system disorders				Hypersensitivity including rash, urticaria and angioedema
Psychiatric disorders	Depressed mood/Depression Nervousness Decreased libido			
Nervous system disorders	Headache Migraine			
Gastrointestinal disorders	Abdominal pain Nausea	Abdominal distension		
Skin and subcutaneous tissue disorders	Acne Hirsutism	Alopecia Pruritus Eczema Chloasma/Skin Hyperpigmentation	Rash	
Musculoskeletal, connective tissue and bone disorders	Back pain			
Reproductive system and breast disorders	Ovarian cysts Pelvic pain Dysmenorrhoea Vaginal discharge Vulvovaginitis Breast tenderness Breast pain	Pelvic inflammatory disease Endometritis Cervicitis/ Papanicolaou smear normal, class II	Uterine perforation	
General disorders and administration site conditions	Intrauterine contraceptive device expelled	Oedema		
Investigations	Weight increase			

				Blood pressure increased

Cases of sepsis (including group A streptococcal sepsis) have been reported following IUD insertion (see section 4.4).

When a woman becomes pregnant with Mirena in situ, the relative risk of ectopic pregnancy is increased (see sections 4.4 and 4.6)

Cases of breast cancer have been reported in Mirena users (see section 4.4).

Clinical trials with Mirena excluded breastfeeding women. A large post authorisation safety study shows an increased risk of perforation in breastfeeding women (see section 4.4).

The following adverse reactions have been reported in connection with the insertion or removal procedure of Mirena: pain, bleeding and insertion-related vasovagal reaction with dizziness or syncope (see section 4.4). The procedure may also precipitate a seizure in patients with epilepsy.

The removal threads may be felt by the partner during intercourse.

4.9 Overdose

Not applicable.

5. Pharmacological properties

5.1 Pharmacodynamic properties

ATC Code: G02BA03

Pharmacotherapeutic group: Plastic IUD with progestogen

Levonorgestrel is a progestogen used in gynaecology in various ways: as the progestogen component in oral contraceptives, in hormonal replacement therapy or alone for contraception in minipills and subdermal implants. Levonorgestrel can also be administered directly into the uterine cavity as an intrauterine system. This allows a very low daily dosage, as the hormone is released directly into the target organ.

The contraceptive mechanism of action of Mirena is based on mainly hormonal effects producing the following changes:

- Prevention of proliferation of the endometrium
- Thickening of the cervical mucus thus inhibiting the passage of sperm
- Suppression of ovulation in some women.

The physical presence of the system in the uterus would also be expected to make a minor contribution to its contraceptive effect.

When inserted according to the insertion instructions, Mirena has a contraceptive failure rate of approximately 0.2% (95% CI: 0.1-0.3) per year and a cumulative failure rate of approximately 0.7% at 5 years. The failure rate may increase in case of Mirena expulsion or perforation.

Mirena may be particularly useful for contraception in patients with excessive menstrual bleeding, and can be successfully used in the treatment of idiopathic menorrhagia. Results from three comparative studies indicate that in menorrhagic women, menstrual blood loss decreased by 62-94% at the end of three months and by 71-95% at the end of six months of use. Mirena appears to have similar effects to endometrial ablation/resection in reducing the menstrual blood loss up to two years. Menorrhagia caused by submucosal fibroids may respond less favourably. Reduced bleeding promotes the increase of blood haemoglobin in patients with menorrhagia.

In idiopathic menorrhagia, prevention of proliferation of the endometrium is the probable mechanism of action of Mirena in reducing blood loss.

The efficacy of Mirena in preventing endometrial hyperplasia during continuous oestrogen treatment is the same when oestrogen is administered orally or transdermally. The observed hyperplasia rate under oestrogen therapy alone is as high as 20%. In clinical studies with a total of 634 perimenopausal and postmenopausal users of Mirena, no cases of endometrial hyperplasia were reported up to four years.

Bleeding Patterns:

Different kinds of bleeding changes (frequent, prolonged or heavy bleeding, spotting, oligomenorrhoea, amenorrhoea) are experienced by all users of Mirena. In fertile women the average number of spotting days/month decreases gradually from nine to four days during the first six months of use. The percentage of women with prolonged bleeding (more than eight days) decreases from 20% to 3% during the first three months of use. In clinical studies during the first year of use, 17% of women experienced amenorrhoea of at least three months duration.

When used in combination with oestrogen replacement therapy, perimenopausal users of Mirena may experience spotting and irregular bleeding during the first months of the treatment. The amount of bleeding becomes minimal during the first year, and 30-60% of users are totally free of bleedings.

5.2 Pharmacokinetic properties

The initial release of levonorgestrel from Mirena is 20 micrograms/24 hours, delivered directly into the uterine cavity. Because of the low plasma concentrations, there are only minor effects on the metabolism.

The pharmacokinetics of levonorgestrel itself have been extensively investigated and reported in the literature. In postmenopausal users of Mirena who were receiving non-oral concomitant oestrogen, plasma levonorgestrel concentrations have been 276 ±119 pg/ml, 196 ± 87pg/ml and 177 ± 70 pg/ml at 56 weeks, 24 months and 48 months respectively. A half life of 20 hours is considered the best estimate although some studies have reported values as short as 9 hours and others as long as 80 hours. Another important finding, although one in agreement with experience with other synthetic steroids, has been marked differences in metabolic clearance rates among individuals, even when administration was by the intravenous route. Levonorgestrel is extensively bound to proteins (mainly sex hormone binding globulin (SHBG) and extensively metabolised to a large number of inactive metabolites.

5.3 Preclinical safety data

Levonorgestrel is a well established progestogen with anti-oestrogenic activity. The safety profile following systemic administration is well documented. A study in monkeys with intrauterine delivery of levonorgestrel for 12 months confirmed local pharmacological activity with good local tolerance and no signs of systemic toxicity. No embryotoxicity was seen in the rabbit following intrauterine administration of levonorgestrel.

6. Pharmaceutical particulars

6.1 List of excipients

Polydimethylsiloxane elastomer

Polydimethylsiloxane tubing

Polyethylene

Barium sulphate

Iron oxide

6.2 Incompatibilities

None known

6.3 Shelf life

Three years

6.4 Special precautions for storage

Not applicable.

6.5 Nature and contents of container

The product is individually packed into a thermoformed blister package with a peelable lid.

6.6 Special precautions for disposal and other handling

Mirena is supplied in a sterile pack which should not be opened until required for insertion. Each system should be handled with aseptic precautions. If the seal of the sterile envelope is broken, the system inside should be disposed of in accordance with the local guidelines for the handling of biohazardous waste. Likewise, a removed Mirena and inserter should be disposed of in this manner. The outer carton package and the inner blister package can be handled as household waste.

7. Marketing authorisation holder

Bayer plc

Bayer House

Strawberry Hill

Newbury

Berkshire RG14 1JA

8. Marketing authorisation number(s)

PL 00010/0547

9. Date of first authorisation/renewal of the authorisation

1 May 2008

10. Date of revision of the text

03 June 2013

Company Contact Details

Bayer plc
http://www.bayer.co.uk

Address
Bayer House, Strawberry Hill, Newbury, Berkshire, RG14 1JA

Telephone
+44 (0)1635 563 000

Fax
+44 (0)1635 563 393

APPENDIX 3: SmPC for LNG-IUS (Levosert) - Updated 31st March 2015

1. Name of the medicinal product
Levosert 20 micrograms/24 hours Intrauterine Delivery System

2. Qualitative and quantitative composition
The active substance is Levonorgestrel.

The intrauterine delivery system contains 52 mg levonorgestrel. The initial release of levonorgestrel is approximately 20 micrograms per day reducing to approximately 12 micrograms per day after 3 years.

For the full list of excipients, see section 6.1

3. Pharmaceutical form
Levonorgestrel Intrauterine delivery system (IUS).

The product consists of an inserter and levonorgestrel IUS, which is loaded at the tip of the inserter. Inserter components are an insertion tube, plunger, flange, body and slider. The device consists of a white or almost white hormone-elastomer core, mounted on a T-body and covered in opaque tubing, which regulates the release of levonorgestrel. The T-body has a loop at one end and two arms at the other end. Removal threads are attached to the loop.

4. Clinical particulars
4.1 Therapeutic indications
Contraception.

Heavy menstrual bleeding. Levosert may be particularly useful in women with heavy menstrual bleeding requiring (reversible) contraception.

4.2 Posology and method of administration

Starting treatment
In women of fertile age, Levosert is inserted into the uterine cavity within seven days of the onset of menstruation. It can be replaced by a new system at any time of the cycle.

Post-partum insertion: To reduce the risk of perforation, postpartum insertions should be postponed until the uterus is fully involuted. Do not insert earlier than six weeks after delivery. If the patient is experiencing significant post-partum bleeding and/or pain then infection or other causes should be excluded before insertion. Levosert can also be inserted immediately after the first trimester abortion.

Levosert is effective for three years in the indications for contraception and heavy menstrual bleeding. Therefore it should be removed after 3 years of use. If the user wishes to continue using the same method, a new system can be inserted at the same time, in which case no additional protection is required.

Before insertion, the patient must be informed about the efficacy, risks and side-effects of Levosert. A gynaecological examination, including examination of the breasts and exclusion of a pregnancy, should be performed. Cervical infection and sexually transmitted diseases should be excluded. The position of the uterus and the size of the uterine cavity should be determined. The instructions for insertion should be followed carefully. The patient should be re-examined six weeks after insertion and once a year thereafter, or more frequently if clinically indicated. Levosert is not indicated for use before menarche.

Paediatric population

Levosert has not been studied in patients below 16 years of age.

Instructions for use and handling
Levosert is supplied in a sterile pack which should not be opened until required for insertion. The exposed product should be handled with aseptic precautions. If the seal of the sterile package is broken, the product should be discarded (see Section 6.6 for disposal instructions).

How to insert Levosert
It is recommended that Levosert should only be inserted by physicians/health care professionals who are experienced in levonorgestrel IUS insertions and/or have undergone sufficient training for levonorgestrel IUS insertion.

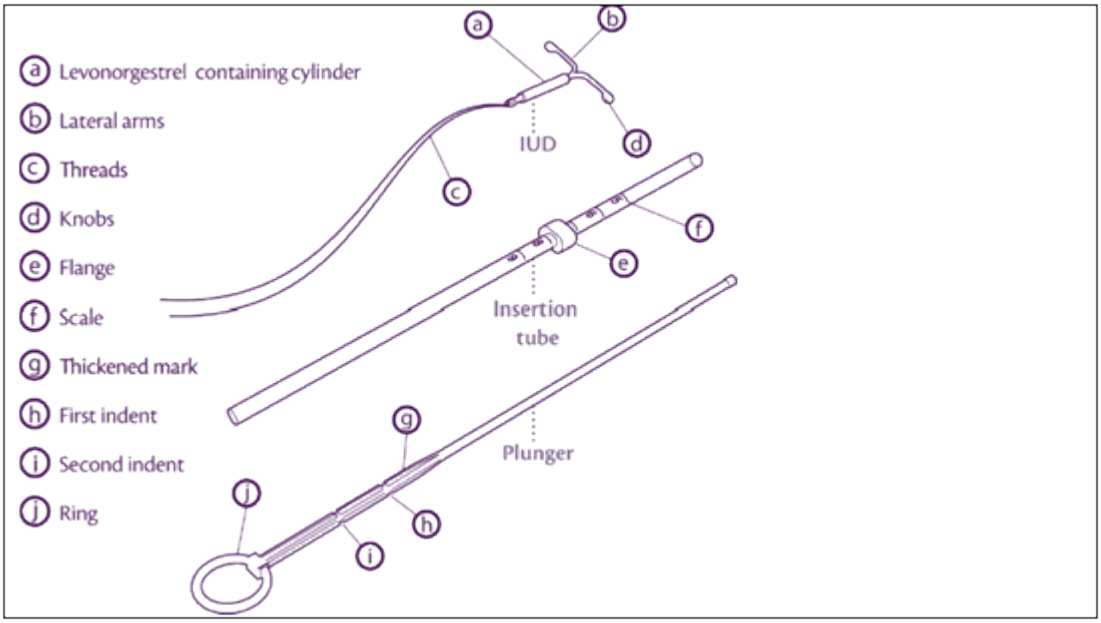
In case of difficult insertion and/or exceptional pain or bleeding during or after insertion, please refer to section 4.4.

• Levosert is supplied sterile having been sterilised with ethylene oxide. Do not resterilise. For single use only. Do not use if the inner package is damaged or open. Insert before the month shown on the label.

• Levosert is inserted with the provided inserter (figure 1) into the uterine cavity by carefully following the insertion instructions.

The following insertion instruction will be provided in the box containing the IUS.

Description



Conditions for use

1. In women of fertile age, Levosert is inserted within seven days of the onset of menstruation. It can be replaced by a new system at any time of the cycle.

2. It is recommended that Levosert should only be inserted by physicians/health care professionals who have undergone sufficient training and have read carefully these instructions before Levosert insertion.

3. Levosert is supplied in a sterile pack. Do not use if the inner package is damaged or open.

4. Determine the position (anteversion, retroversion) and size of the uterus by a gynaecological examination. Exclude pregnancy and contraindications.

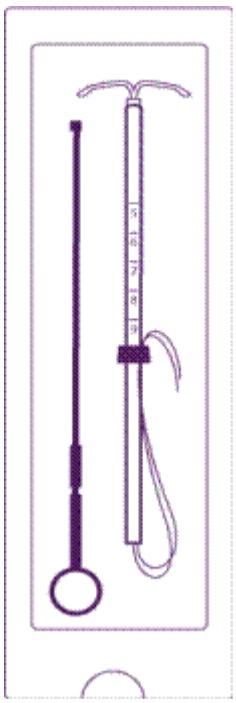
5. Place a speculum, use appropriate antiseptic solution to clean the vagina and cervix.

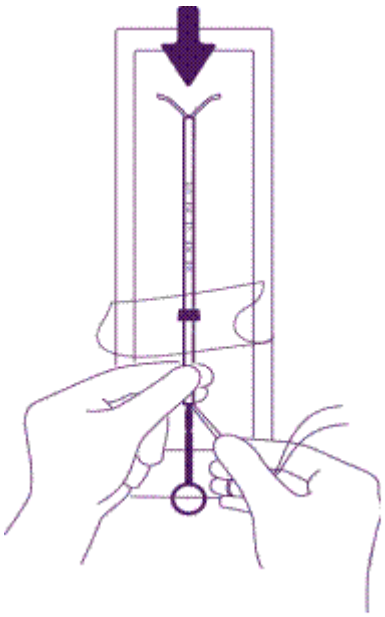
6. Use cervical dilators if cervical stenosis is diagnosed. Do not force to overcome resistance.

7. Grasp the cervix with a Tenaculum forceps and apply a gentle traction in order to straighten alignment of the cervical canal and uterine cavity.

8. Determine the uterine depth by hysterometry. If uterine depth is < 5.5 cm discontinue the procedure.

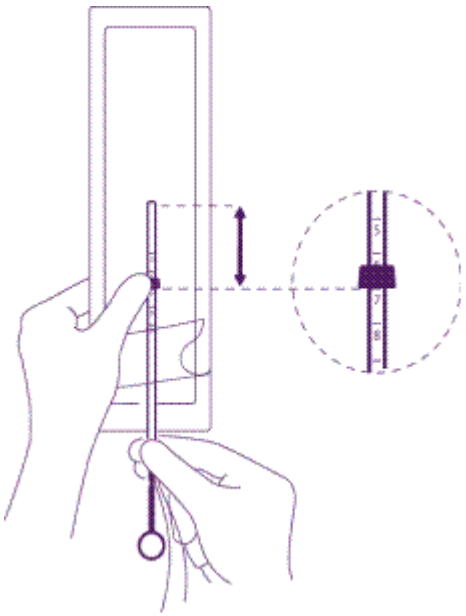
Preparation for insertion





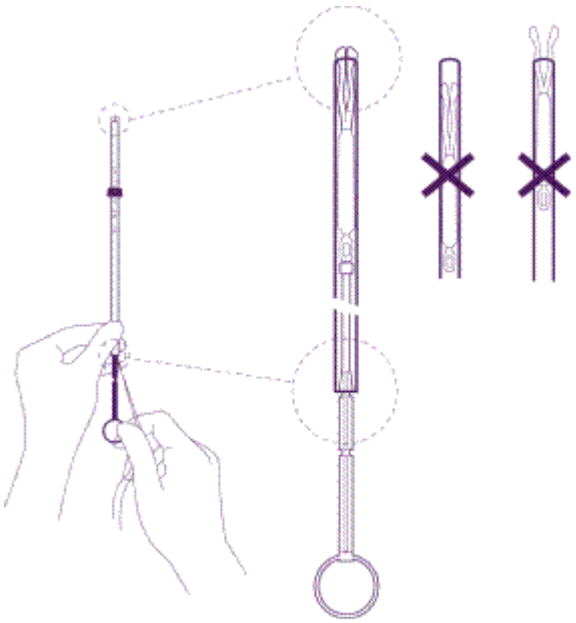
Introduce the plunger and the IUD in the insertion tube

Partly open the blister (about 1/3 from the bottom) and introduce the plunger in the insertion tube. Extricate the threads from the flange. Pull the thread to introduce the IUD into the tube. The arms of the IUD must stay in an horizontal plan, parallel to the flat side of the flange.



Position the lower edge of the flange at the sounded value

Position the blue flange so as the lower edge of the flange indicates the value found by hysterometry. The flat sides of the flange must always remain parallel to the arms. This will allow the arms to open correctly in the uterine cavity.

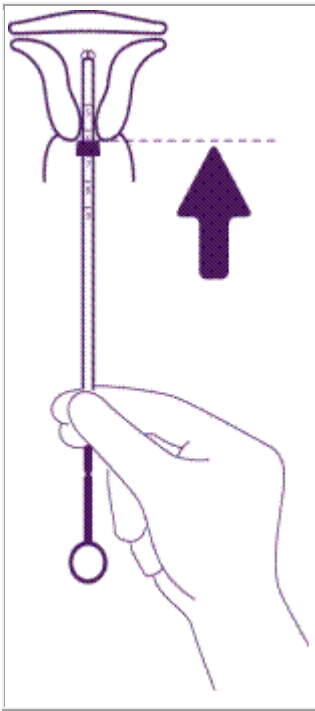


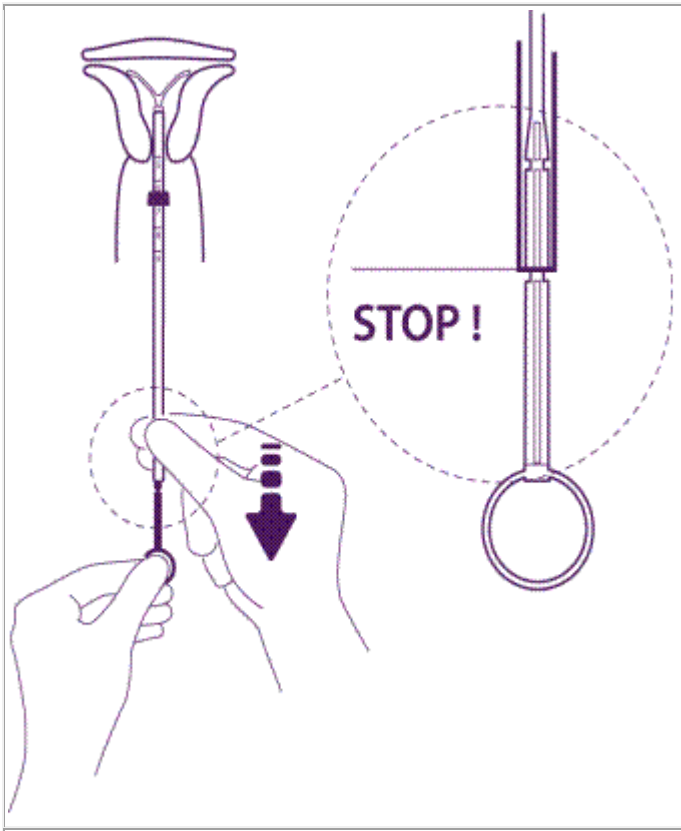
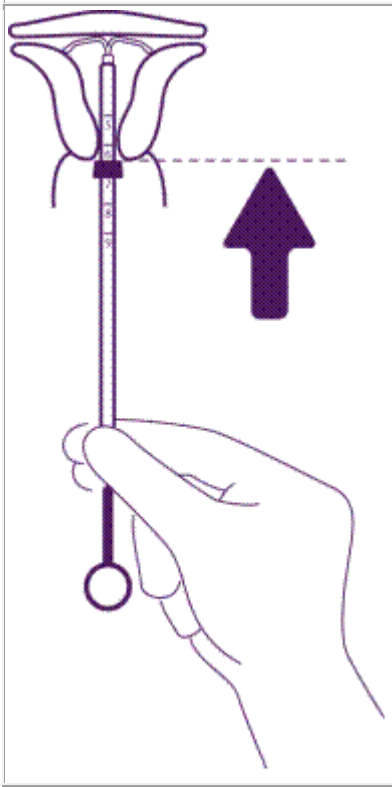
Adjust the position of the IUD in the insertion tube

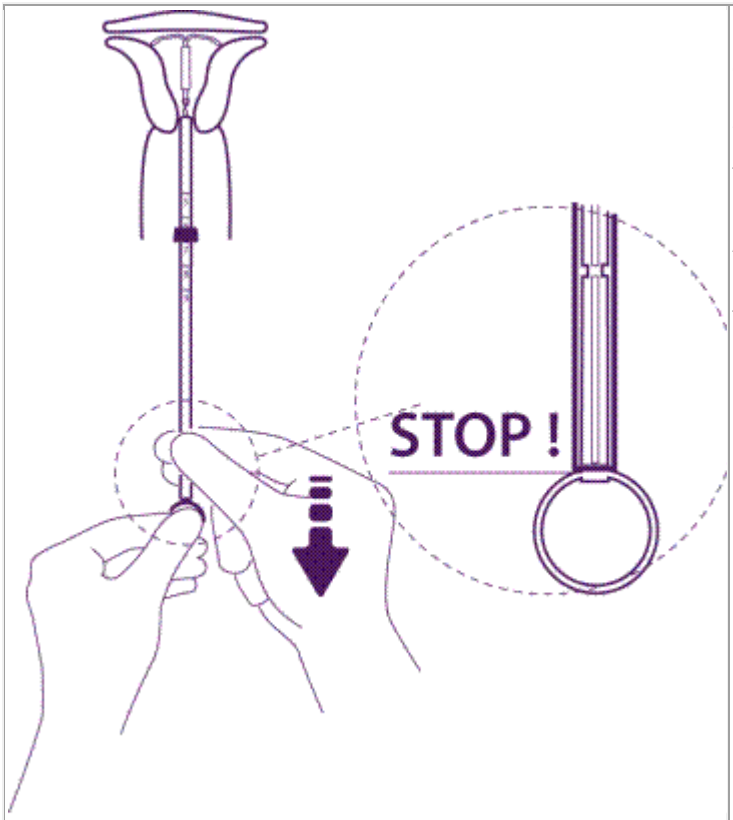
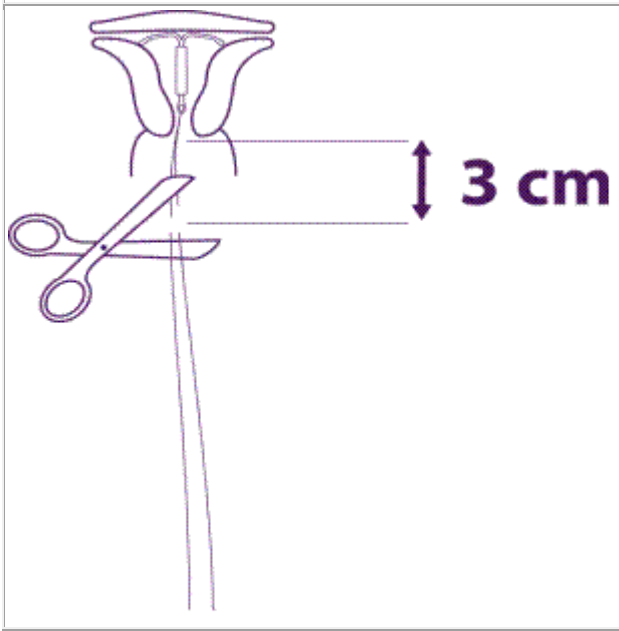
Hold the plunger firmly while pulling the thread and moving the tube to adjust the IUD´s position.

The knobs of the lateral arms must be closely opposed to each other, slightly above the upper extremity of the insertion tube (see zoom 1) and the distal edge of the tube must be aligned with the first indent of the plunger (see zoom 2). If the tube is not aligned with the first indent of the plunger you must pull the thread more firmly.

Insertion

	Introduce the device in the cervical canal until the blue flange is in contact with the cervix Take the whole device out of the blister, by holding firmly the plunger and tube together in the correctly adjusted position. Introduce the assembly into the cervical canal until the blue flange is in contact with the cervix.

	*Release the arms of the intrauterine device* Hold the plunger, release the thread and pull the insertion tube down until its lower extremity reaches the second indent of the plunger.
	*Push the IUD against the fundus* To position the IUD in the uterine cavity, push the insertion tube simultaneously with the plunger, until the blue flange is again in contact with the cervix. Levosert is then correctly placed in the uterine cavity.

	*Release the IUD from the tube into the uterine cavity* Without moving the plunger, pull the insertion tube down to the ring of the plunger. A slight resistance marks the passage of the bulge of the plunger. Nevertheless pull down the tube to the ring of the plunger. Levosert is then released completely from the insertion tube.
	*Remove sequentially the inserter components and cut the threads* Remove sequentially, first the plunger, then the insertion tube. Cut the threads at around 3 cm from the cervix.

IMPORTANT!
In case of difficult insertion and/or exceptional pain or bleeding during or after insertion, physical examination and ultrasound should be performed immediately to exclude perforation of the uterine body or cervix. If necessary remove the system and insert a new, sterile system.

Please report to our pharmacovigilance department any case of uterine perforation or insertion difficulties : Actavis UK Ltd. E-mail: medinfo@actavis.co.uk Phone: 01271 385257.

How to remove Levosert

Levosert is removed by gently pulling on the threads with forceps. If the threads are not visible and the device is in the uterine cavity, it may be removed using a narrow tenaculum. This may require dilatation of the cervical canal.

After removal of Levosert, the device should be checked to ensure it is intact. During difficult removals, single cases have been reported of the hormone cylinder sliding over the horizontal arms and hiding them inside the cylinder. This situation does not require further intervention once completeness of the IUS has been ascertained. The knobs of the horizontal arms usually prevent complete detachment of the cylinder from the T-body.

4.3 Contraindications
- Known or suspected pregnancy
- Current or recurrent pelvic inflammatory disease
- Current genital infection
- Postpartum endometritis
- Infected abortion during the past three months
- Cervicitis, Cervical dysplasia
- Suspected or confirmed uterine or cervical malignancy
- Liver tumour or other acute or severe liver disease
- Congenital or acquired abnormality of the uterus including fibroids if they distort the uterine cavity
- Undiagnosed abnormal genital bleeding
- Conditions associated with increased susceptibility to infections
- Active or previous severe arterial disease, such as stroke or myocardial infarction
- Current or suspected hormone dependent tumours such as breast cancer (see section 4.4)
- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Acute malignancies affecting the blood or leukaemias except when in remission
- Recent trophoblastic disease while hCG levels remain elevated

4.4 Special warnings and precautions for use
Medical examination
Before insertion, a complete personal and family medical history should be taken. Physical examination should be guided by this and by the contraindications and warnings for use. Pulse and blood pressure should be measured and a bimanual pelvic examination performed to establish the orientation of the uterus. The patient should be re-examined six weeks after insertion and further examinations should be performed where clinically indicated and adapted to the individual woman rather than as routine procedure. Prior to insertion pregnancy should be excluded and genital infection should be successfully treated. Women should be advised that Levosert does not protect against HIV (AIDs) and other sexually transmitted disease (please refer to the section below on pelvic infections).

Women should be encouraged to attend cervical and breast screening as appropriate for their age.

Conditions under which Levosert can be used with caution
Levosert may be used with caution after specialist consultation, or removal of the system should be considered, if any of the following conditions exist or arise for the first time during treatment:

Migraine with aura

Unusually severe or unusually frequent headache

Jaundice

Marked increase of blood pressure

Malignancies affecting the blood or leukaemias in remission

Use of chronic corticosteroid therapy

Past history of symptomatic functional ovarian cysts

Active or previous severe arterial disease, such as stroke or myocardial infarction

Severe or multiple risk factors for arterial disease

Thrombotic arterial or any current embolic disease

Venous thromboembolism.

In general, women using Levosert should be encouraged to stop smoking.

Insertion / removal warnings and precautions
General Information: Insertion and removal may be associated with some pain and bleeding. In case of difficult insertion and/or exceptional pain or bleeding during or after insertion, physical examination and ultrasound should be performed immediately to exclude perforation of the uterine corpus or cervix (see also 'Perforation').
The procedure may precipitate fainting as a vasovagal reaction or a seizure in an epileptic patient. In the event of early signs of a vasovagal attack, insertion may need to be abandoned or the system removed. The woman should be kept supine, the head lowered and the legs elevated to the vertical position if necessary in order to restore cerebral blood flow. A clear airway must be maintained; an airway should always be at hand. Persistent bradycardia may be controlled with intravenous atropine. If oxygen is available it may be administered.

Perforation: Perforation of the uterine corpus or cervix may occur, most commonly during insertion. This may be associated with severe pain and continued bleeding. If perforation is suspected the system should be removed as soon as possible. The risk of perforation may be increased in post-partum insertions (see section 4.2), in lactating women and in women with a fixed retroverted uterus.

Pelvic infection: Known risk factors for pelvic inflammatory disease are multiple sexual partners, frequent intercourse and young age. Pelvic infection may have serious consequences as it may impair fertility and increase the risk of ectopic pregnancy.

For women using Levosert with symptoms and signs suggestive of pelvic infection appropriate antibiotics should be started. There is no need to remove Levosert unless the symptoms fail to resolve within the following 72 hours or unless the women wishes Levosert to be removed. Levosert must be removed if the women experiences recurrent endometritis or pelvic infection, or if an acute infection is severe.

Complications leading to failure
Expulsion: Symptoms of the partial or complete expulsion of any IUS may include bleeding or pain. However, a system can be expelled from the uterine cavity without the woman noticing it. Partial expulsion may decrease the effectiveness of Levosert. As the device decreases menstrual flow, increase of menstrual flow may be indicative of an expulsion. A displaced Levosert should be

removed and a new system inserted. The woman should be advised how to check the threads of Levosert.

Lost threads: If the retrieval threads are not visible at the cervix on follow-up examination, first exclude pregnancy. The threads may have been drawn up into the uterus or cervical canal and may reappear during the next menstrual period. If pregnancy has been excluded, the threads may usually be located by gently probing with a suitable instrument. If they cannot be found, they may have broken off, or the device may have been expelled. Ultrasound or X-ray may be used to locate the IUS.

Bleeding irregularities
Irregular bleeding: Levosert usually achieves a significant reduction in menstrual blood loss within 3 to 6 months of treatment. Increased menstrual flow or unexpected bleeding may be indicative of expulsion. If menorrhagia persists then the woman should be re-examined. An assessment of the uterine cavity should be performed using ultrasound scan. An endometrial biopsy should also be considered.

Because irregular bleeding/spotting may occur during the first months of therapy in pre-menopausal women, it is recommended to exclude endometrial pathology before insertion of Levosert.

When to check for pregnancy in women of child bearing potential: The possibility of pregnancy should be considered if menstruation does not occur within six weeks of the onset of previous menstruation and expulsion should be excluded. A repeated pregnancy test is not necessary in amenorrhoeic subjects unless indicated by other symptoms.

Treatment review advice for Menorrhagia: Levosert usually achieves a significant reduction in menstrual blood loss within 3 to 6 months of treatment. If significant reduction in blood loss is not achieved in these time-frames, alternative treatments should be considered.

Other risks during use
Ectopic pregnancy: The absolute risk of ectopic pregnancy in users of levonorgestrel IUS is low. However, when a woman becomes pregnant with Levosert in situ, the relative likelihood of ectopic pregnancy is increased. The possibility of ectopic pregnancy should be considered in the case of lower abdominal pain - especially in connection with missed periods or if an amenorrhoeic woman starts bleeding. The rate of ectopic pregnancy in users of levonorgestrel IUS is 0.06 per 100 woman-years. This rate is lower than the rate of 0.3-0.5 per 100 woman-years estimated for women not using any contraception. The corresponding figure for the copper IUS is 0.12 per 100 woman years. Women with a previous history of ectopic pregnancy carry a higher risk of a further ectopic pregnancy.

Ovarian Cysts: Ovulatory cycles with follicular rupture usually occur in women of fertile age. Sometimes atresia of the follicle is delayed and folliculogenesis may continue. These enlarged follicles cannot be distinguished clinically from ovarian cysts. Data from clinical trials suggest that ovarian cysts have been reported as an adverse drug reaction in approximately 7% of women using Levosert, however some published studies have reported a higher incidence of ovarian cysts (which could have been influenced by factors including frequency and criteria of ultrasound scanning, and patient population). Most of these follicles are asymptomatic, although some may be accompanied by pelvic pain or dyspareunia.

In most cases, the ovarian cysts disappear spontaneously during two to three months observation. Should this not happen, continued ultrasound monitoring and other diagnostic/therapeutic measures are recommended. Rarely, surgical intervention may be required.

Breast cancer: A meta-analysis from 54 epidemiological studies reported that there is a slightly increased relative risk (RR = 1.24) of having breast cancer diagnosed in women who are currently using combined oral contraceptives (COCs), mainly using oestrogen-progestogen preparations. The excess risk gradually disappears during the course of the 10 years after cessation of COC use. Because breast cancer is rare in women under 40 years of age, the excess number of breast cancer diagnoses in current and recent COC users is small in relation to the overall risk of breast cancer. The risk of having breast cancer diagnosed in users of progestogen-only methods (POPs, implants and injectables), including Levosert, is possibly of similar magnitude to that associated with COC. However, for progestogen-only contraceptive preparations, the evidence is based on much smaller populations of users and so is less conclusive than that for COCs.

General Information
Glucose tolerance: Low-dose levonorgestrel may affect glucose tolerance and blood glucose concentrations should be monitored in diabetic users of Levosert.

4.5 Interaction with other medicinal products and other forms of interaction
The effects of Levosert may be impaired by drugs which induce liver enzymes, including barbiturates, primidone, phenytoin, carbamazepine, griseofulvin and rifampicin. No interaction studies on the influence of these drugs on the efficacy of Levosert have been performed.

4.6 Fertility, pregnancy and lactation
Pregnancy: Levosert is not to be used during an existing or suspected pregnancy. In case of an accidental pregnancy with Levosert in situ (see section 5: pharmacological properties), ectopic pregnancy should be excluded (see section 4.4) and the system must be removed and termination of the pregnancy should be considered as there is a high risk for pregnancy complications (abortion, infection and sepsis). Removal of Levosert or probing of the uterus may result in spontaneous abortion. Should these procedures not be possible, the woman should be informed about these risks, and accordingly, such pregnancies should be closely monitored. The woman should be instructed to report all symptoms that suggest complications of the pregnancy, like cramping abdominal pain with fever.

Local exposure to levonorgestrel:
Clinical experience of the outcomes of pregnancies with levonorgestrel IUS in situ is limited. However, to date, there is no evidence of birth defects caused by local levonorgestrel IUS use in cases where pregnancy continues to term with the IUS in place.
Breastfeeding: Levonorgestrel is excreted in very small quantities in breast milk after use in levonorgestrel IUS. Since no risk for the child is expected, breast feeding can be continued during use of Levosert.
Uterine bleeding has rarely been reported in women using a levonorgestrel IUS during lactation.
Fertility: the use of levonorgestrel IUS does not alter the course of female fertility after removal of the IUS.

4.7 Effects on ability to drive and use machines
Levosert has no known influence on the ability to drive or use machines.

4.8 Undesirable effects

Undesirable effects are more common during the first months after the insertion, and subside during prolonged use.

Very common undesirable effects (occurring in more than 10% of users) include uterine/vaginal bleeding including spotting, oligomenorrhoea, amenorrhoea (see section 5.1) and benign ovarian cysts.

The frequency of benign ovarian cysts depends on the diagnostic method used, and in clinical trials enlarged follicles have been diagnosed in 12% of the subjects using a levonorgestrel IUS. Most of the follicles are asymptomatic and disappear within three months.

Organ system	***Undesirable effects***			
	Very common: ≥1/10	**Common: ≥1/100 to <1/10**	**Uncommon: ≥1/1000 to <1/100**	**Rare: ≥1/10000 to <1/1000**
Psychiatric disorders		Depressive mood Nervousness Decreased libido	Altered mood	
Nervous system disorders		Headache	Migraine	
Gastrointestinal disorders		Abdominal pain Nausea	Abdominal distension	
Skin and subcutaneous tissue disorders		Acne	Alopecia Hirsutism Pruritus Eczema	Rash Urticaria
Musculoskeletal and connective tissue disorders		Back pain		
Reproductive system and breast disorders	Bleeding changes Benign ovarian cysts	Pelvic pain Dysmenorrhoea Vaginal discharge vulvovaginitis Breast tendenress Breast pain	Pelvic Inflammatory disease Endometritis Cervicitis Papanicolaou smear normal, class II	Uterine perforation
General disorders and administration site conditions		Intrauterine contraceptive device expelled	Oedema	
Investigations		Weight increase		

When a woman becomes pregnant with Levosert in situ, the relative risk of ectopic pregnancy is increased (see 'Special warnings and precautions for use' and 'Fertility, pregnancy and lactation').

In addition, cases of breast cancer have been reported in levonorgestrel IUS users (frequency unknown, see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare

professionals are asked to report any suspected adverse reactions via the national reporting system listed in Yellow Card Scheme
Website: www.mhra.gov.uk/yellowcard

4.9 Overdose
Not applicable.

5. Pharmacological properties
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Intrauterine contraceptives, plastic IUD with progestogen ATC code: G02BA03

Levonorgestrel is a progestogen used in gynaecology in various ways: as the progestogen component in oral contraceptives, in hormonal replacement therapy or alone for contraception in minipills and subdermal implants. Levonorgestrel can also be administered directly into the uterine cavity as an IUS. This allows a very low daily dosage, as the hormone is released directly into the target organ.

The contraceptive mechanism of action of the levonorgestrel IUS is based mainly on hormonal effects producing the following changes:

- Prevention of proliferation of the endometrium
- Thickening of the cervical mucus thus inhibiting the passage of sperm
- Suppression of ovulation in some women.

The physical presence of the system in the uterus would also be expected to make a minor contribution to its contraceptive effect.
When inserted according to the insertion instructions, Levosert has a contraceptive failure rate of approximately 0.19% (95% CI: 0.05% - 0.75%) per year. The failure rate may increase in case of the Levosert expulsion or perforation.

Levonorgestrel IUS may be particularly useful for contraception in patients with heavy menstrual bleeding, and can be successfully used in the treatment of idiopathic menorrhagia.
The volume of menstrual bleeding was decreased by 88% in menorrhagic women by the end of three months of use. Menorrhagia caused by submucosal fibroids may respond less favourably. Reduced bleeding promotes the increase of blood haemoglobin in patients with menorrhagia.
In idiopathic menorrhagia, prevention of proliferation of the endometrium is the probable mechanism of action of levonorgestrel IUS in reducing blood loss.

Bleeding Patterns:
Different kinds of bleeding changes (frequent, prolonged or heavy bleeding, spotting, oligomenorrhea, amenorrhoea) are experienced by all users of levonorgestrel IUS. In fertile women the average number of spotting days/month decreases gradually from nine to four days during the first six months of use. The percentage of women with prolonged bleeding (more than eight days) decreases from 20% to 3% during the first three months of use. In clinical studies during the first year of use, 17% of women experienced amenorrhoea of at least three months duration.

5.2 Pharmacokinetic properties
The initial release of levonorgestrel from Levosert is 20 micrograms/24 hours, delivered directly into the uterine cavity. Because of the low plasma concentrations, there are only minor effects on the metabolism.

The pharmacokinetics of levonorgestrel itself have been extensively investigated and reported in the literature. A half life of 20 hours is considered the best estimate although some studies have reported values as short as 9 hours and others as long as 80 hours. Another important finding, although one in agreement with experience with other synthetic steroids, has been marked differences in metabolic clearance rates among individuals, even when administration was by the intravenous route. Levonorgestrel is extensively bound to proteins (mainly sex hormone binding globulin [SHBG]) and extensively metabolised to a large number of inactive metabolites.

5.3 Preclinical safety data
Non-clinical data reveal no special hazard for humans other than the information already included in other sections of the SmPC. These data are based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential and toxicity to reproduction and development.

6**. Pharmaceutical particulars**
6.1 List of excipients
Silicone base
Tetra-n-propyl silicate
Stannous octoate
Polydimethylsiloxane elastomer
Polydimethylsiloxane tubing
Polyethylene T-frame with 20-24% barium sulphate
Polypropylene thread
Copper phthalocyanine blue

6.2 Incompatibilities
Not applicable

6.3 Shelf life
48 months

6.4 Special precautions for storage
Store in the original package.

6.5 Nature and contents of container
Levosert IUS with the inserter device is individually packed into a thermoformed blister (polyester) package with a peelable lid (TYVEK-Polyethylene).

6.6 Special precautions for disposal and other handling
As the insertion technique is different from intrauterine devices, special emphasis should be given to training in the correct insertion technique. Special instructions for insertion are in the package. Levosert is supplied in a sterile pack which should not be opened until required for insertion. Each system should be handled with aseptic precautions. If the seal of the sterile envelope is broken, the system inside should be disposed of in accordance with the local guidelines for the handling of biohazardous waste. Likewise, a removed Levosert and inserter should be disposed of in this manner. The outer carton package and the inner blister package can be handled as household waste.

7. Marketing authorisation holder
Actavis Group PTC ehf.

Reykjavíkurvegi 76-78

220 Hafnarfjörður

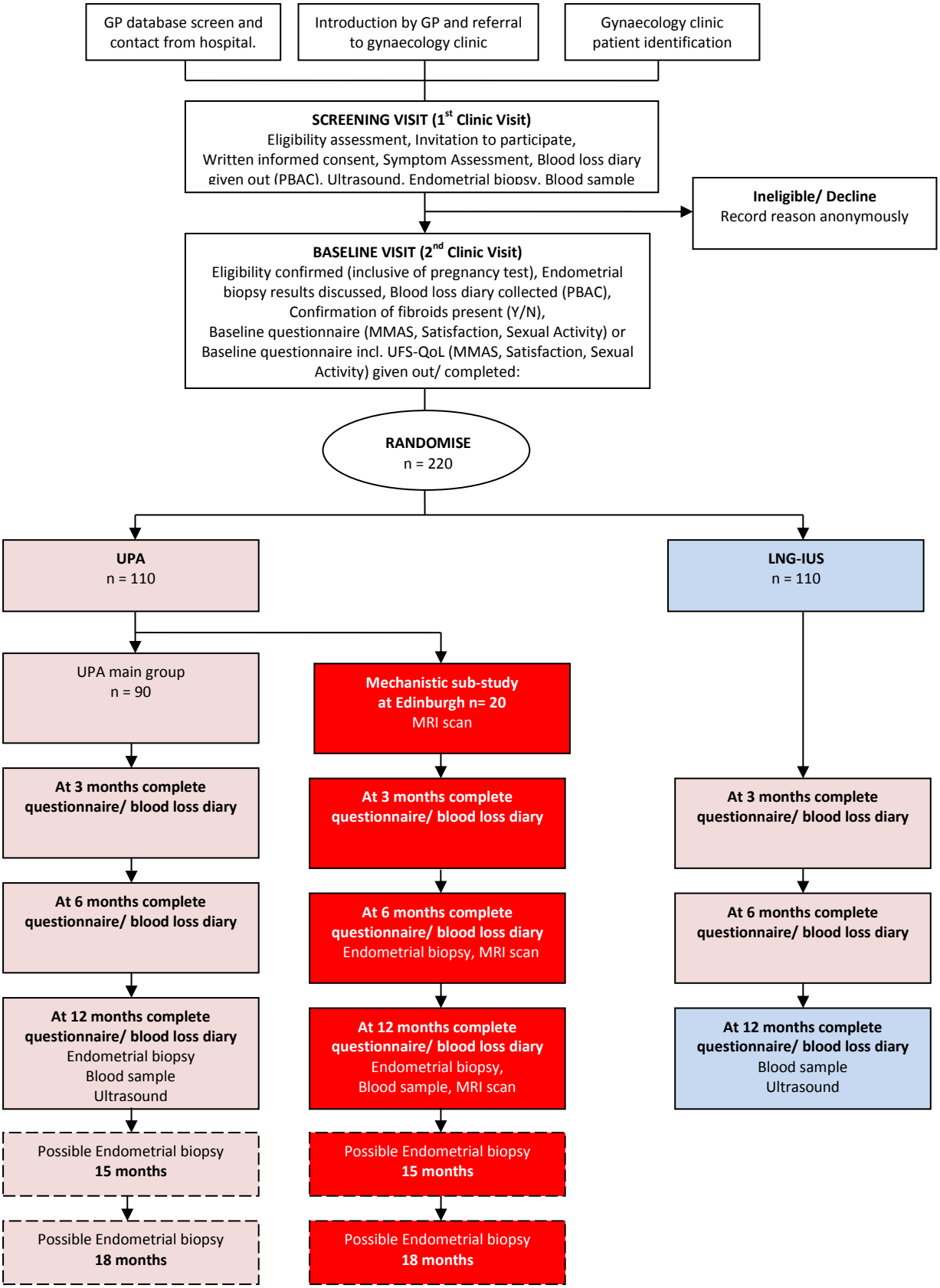
Iceland

8. Marketing authorisation number(s)
PL 30306/0438

9. Date of first authorisation/renewal of the authorisation
28/12/2012

10. Date of revision of the text
23/10/2014

APPENDIX 4: TRIAL SCHEMA



References

1. Rahn DD, Abed H, Sung VW, Matteson KA, Rogers RG, Morrill MY, et al. Systematic review highlights difficulty interpreting diverse clinical outcomes in abnormal uterine bleeding trials. J Clin Epidemiol. 2011;64(3):293-300.

2. Abdel-Aleem H, d'Arcangues C, Vogelsong KM, Gulmezoglu AM. Treatment of vaginal bleeding irregularities induced by progestin only contraceptives. Cochrane Database Syst Rev. 2007(4):CD003449.

3. Gupta J, Kai J, Middleton L, Pattison H, Gray R, Daniels J, et al. Levonorgestrel intrauterine system versus medical therapy for menorrhagia. N Engl J Med. 2013;368(2):128-37.

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

5. 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(5):591-8.

6. 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 Gynecol Pathol. 2012;31(6):556-69.

7. Pohl O, Williams AR, Bergeron C, Gotteland JP. A 39-week oral toxicity study of ulipristal acetate in cynomolgus monkeys. Regul Toxicol Pharmacol. 2013;66(1):6-12.

8. Mutter GL, Ince TA, Baak JP, Kust GA, Zhou XP, Eng C. Molecular identification of latent precancers in histologically normal endometrium. Cancer Res. 2001;61(11):4311-4.

9. Daikoku T, Hirota Y, Tranguch S, Joshi AR, DeMayo FJ, Lydon JP, et al. Conditional loss of uterine Pten unfailingly and rapidly induces endometrial cancer in mice. Cancer Res. 2008;68(14):5619-27.

10. Mutter GL, Lin MC, Fitzgerald JT, Kum JB, Baak JP, Lees JA, et al. Altered PTEN expression as a diagnostic marker for the earliest endometrial precancers. J Natl Cancer Inst. 2000;92(11):924-30.

11. Orbo A, Rise CE, Mutter GL. Regression of latent endometrial precancers by progestin infiltrated intrauterine device. Cancer Res. 2006;66(11):5613-7.

12. Zheng W, Baker HE, Mutter GL. Involution of PTEN-null endometrial glands with progestin therapy. Gynecol Oncol. 2004;92(3):1008-13.

13. Shaw RW, Brickley MR, Evans L, Edwards MJ. Perceptions of women on the impact of menorrhagia on their health using multi-attribute utility assessment. Br J Obstet Gynaecol. 1998;105(11):1155-9.

14. Higham JM, O'Brien PM, Shaw RW. Assessment of menstrual blood loss using a pictorial chart. Br J Obstet Gynaecol. 1990;97(8):734-9.

15. Spies JB, Coyne K, Guaou Guaou N, Boyle D, Skyrnarz-Murphy K, Gonzalves SM. The UFS-QOL, a new disease-specific symptom and health-related quality of life questionnaire for leiomyomata. Obstet Gynecol. 2002;99(2):290-300.

16. Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res. 2011;20(10):1727-36.

17. Al-Janabi H, Coast J. ICECAP-A measure V2. Social Science and Medicine. 2008.

18. Thirlaway K, Fallowfield L, Cuzick J. The Sexual Activity Questionnaire: a measure of women's sexual functioning. Qual Life Res. 1996;5(1):81-90.