

Ulipristal acetate versus conventional management of heavy menstrual bleeding

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| Submission date 25/03/2015 | Recruitment status No longer recruiting | <input checked="" type="checkbox"/> Prospectively registered <input checked="" type="checkbox"/> Protocol |
| Registration date 25/03/2015 | Overall study status Completed | <input type="checkbox"/> Statistical analysis plan <input checked="" type="checkbox"/> Results |
| Last Edited 23/04/2025 | Condition category Urological and Genital Diseases | <input type="checkbox"/> Individual participant data |

Plain English summary of protocol

Current plain English summary as of 29/05/2020:

Background and study aims

Heavy menstrual bleeding (HMB) refers to when a woman loses an excessive amount of blood over a number of periods. It's not necessarily a symptom of there being something seriously wrong, but it can have a serious effect on a woman's quality of life. Medication is the main treatment, but surgery is also an option for women when other treatment options have failed. There is a pressing need to develop safe, simple, acceptable, fertility-sparing medical treatments for HMB for women regardless of age, reproductive history and the presence of uterine fibroids (non-cancerous growths in the uterus). Limitations of current medical treatments are that they often do not work or have side effects that women find unacceptable. An exciting new class of drugs, called selective progesterone receptor modulators (SPRMs), offer the potential to revolutionise the way we treat HMB by addressing the unmet need of sustainable long term medical therapy.

AIMS: We aim to test the hypothesis that the SPRM, ulipristal acetate (UPA; Esmya®), is more effective than the levonorgestrel-releasing intra-uterine system (LNG-IUS) - Mirena® or LNG-IUS – Levosert for the long-term treatment of HMB. Further, we aim to acquire an understanding of the mechanism of action of UPA on the endometrium and structure of the uterus.

Who can participate?

Woman (aged at least 18) with HMB.

What does the study involve?

Participants are randomly allocated into one of two groups. Those in group 1 are treated with UPA. Those in group 2 are treated with LNG-IUS. The two groups are compared to see whether UPA works better in improving HMB compared with LNG-IUS after 12 months treatment. We also look at bleeding patterns, satisfaction with treatment and safety. Women are asked to complete questionnaires before treatment, and then after 3, 6 and 12 months of treatment.

What are the possible benefits and risks of participating?

The UCON trial is led by a team of experienced researchers, who have an excellent track record of both running clinical trials and investigating menstrual bleeding problems.

Women treated with UPA are monitored for side effects with scans and examining samples from

the womb lining. A subgroup of participants who are taking UPA will also have detailed MR investigations of the womb to study womb structure, along with in depth examination of samples of the womb-lining (endometrium). Ultimately, there could be savings to the NHS from fewer operations to remove the womb (hysterectomy) or destroy its lining (endometrial ablation).

Where is the study run from?

Royal Infirmary of Edinburgh (lead site) and 4 other hospitals in the UK.

When is the study starting and how long is it expected to run for?

October 2014 to May 2021

Who is funding the study?

National Institute for Health Research (UK)

Who is the main contact?

Professor Hilary Critchley, Hilary.Critchley@ed.ac.uk

Previous plain English summary:

Background and study aims

Heavy menstrual bleeding (HMB) refers to when a woman loses an excessive amount of blood over a number of periods. It's not necessarily a symptom of there being something seriously wrong, but it can have a serious effect on a woman's quality of life. Medication is the main treatment, but surgery is also an option for women when other treatment options have failed. There is a pressing need to develop safe, simple, acceptable, fertility sparing medical treatments for HMB for women regardless of age, reproductive history and the presence of uterine fibroids (non-cancerous growths in the uterus). Limitations of current medical treatments are that they often do not work or have side effects that women find unacceptable. An exciting new class of drugs, called selective progesterone receptor modulators (SPRMs), offer the potential to revolutionise the way we treat HMB by addressing the unmet need of sustainable long term medical therapy. Here, we aim to test whether the SPRM ulipristal acetate (UPA; Esmya®), works better than the levonorgestrel-releasing intrauterine system (LNG-IUS, Mirena®) for the long term treatment of HMB.

Who can participate?

Woman (aged at least 18) with HMB.

What does the study involve?

Participants are randomly allocated into one of two groups. Those in group 1 are treated with UPA. Those in group 2 are treated with LNG-IUS. The two groups are compared to see whether UPA works better in improving HMB compared with LNG-IUS after 12 months treatment. We also look at bleeding patterns, satisfaction with treatment and safety. Women are asked to complete questionnaires before treatment, and then after 3, 6 and 12 months of treatment.

What are the possible benefits and risks of participating?

The UCON trial is led by a team of experienced researchers, who have an excellent track record of both running clinical trials and investigating menstrual bleeding problems. Women treated with UPA are monitored for side effects with scans and examining samples from the womb lining, as changes to the womb lining have been noted after 3 months. Furthermore, additional samples are taken from a smaller group of women also have a detailed MR investigation of the womb to measure uterine perfusion. This shows the effect of UPA on structure and blood supply of the uterus both in the presence and absence of fibroids. Ultimately, there could be savings to

the NHS from fewer operations to remove the womb (hysterectomy) or destroy its lining (endometrial ablation).

Where is the study run from?

Royal Infirmary of Edinburgh (lead site) and 4 other hospitals in the UK.

When is the study starting and how long is it expected to run for?

October 2014 to May 2021 (updated 22/05/2020, previously: February 2015 to September 2018)

Who is funding the study?

National Institute for Health Research (UK)

Who is the main contact?

Professor Hilary Critchley

Hilary.Critchley@ed.ac.uk

Study website

<https://www.birmingham.ac.uk/ucon>

Contact information

Type(s)

Scientific

Contact name

Prof Hilary OD Critchley

Contact details

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Hilary.Critchley@ed.ac.uk

Additional identifiers

EudraCT/CTIS number

2014-003408-65

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers

18534

Study information

Scientific Title

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

Acronym

UCON

Study objectives

Current study hypothesis as of 21/05/2020:

The selective progesterone receptor modulator (SPRM) ulipristal acetate (UPA; Esmya®), is more effective than the levonorgestrel-releasing intrauterine system (LNGIUS) for the long term treatment of heavy menstrual bleeding (HMB). We also aim to acquire an understanding of the mechanism of action of UPA on the endometrium and its effects upon the vasculature and structure of the uterus.

Previous study hypothesis:

The selective progesterone receptor modulator (SPRM) ulipristal acetate (UPA; Esmya®), is more effective than the levonorgestrel-releasing intrauterine system (LNGIUS, Mirena®) for the long term treatment of heavy menstrual bleeding (HMB). We also aim to acquire an understanding of the mechanism of action of UPA on the endometrium and its effects upon the vasculature and structure of the uterus.

Ethics approval required

Old ethics approval format

Ethics approval(s)

NRES Committee London - Bloomsbury, 18/11/2014, 14/LO/1602

Study design

Randomised; Interventional; Design type: Treatment

Primary study design

Interventional

Secondary study design

Randomised controlled trial

Study setting(s)

Hospital

Study type(s)

Treatment

Participant information sheet

Not available in web format, please use contact details to request a patient information sheet

Health condition(s) or problem(s) studied

Topic: Reproductive health and childbirth; Subtopic: Reproductive Health and Childb (all Subtopics); Disease: Menstrual Disorders

Interventions

1. Intervention: Ulipristal Acetate (UPA)
2. Reference/ Control group: levonorgestrel-releasing intrauterine system (LNG-IUS)

Treatment duration: 12 months.

Follow-up: 12 month questionnaire. Gynaecology clinic appointment (UPA group receive 12 month ultrasound, blood sample, endometrial biopsy). LNG-IUS Group receive 12 month ultrasound and blood sample).

Intervention Type

Drug

Phase

Phase III

Drug/device/biological/vaccine name(s)

Ulipristal Acetate

Primary outcome measure

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.

Secondary outcome measures

Current secondary outcome measures as of 21/05/2020:

1. Menstrual bleeding will be captured by validated Pictorial Blood Loss Assessment Chart (PBAC)
 2. Cycle regularity and duration
 3. Visual analogue scales (0-10) for pelvic pain during periods, intercourse and at other times.
 4. Sexual Activity Questionnaire, a measure of sexual functioning, used in other HMB trials
 5. General quality of life (EuroQoL – EQ-5D-5L) and ICECAP-A)
 6. Satisfaction with treatment on a 5-point Likert scale
 7. Participant rating of effect of treatment on HMB over 12 months measured on a 4-point Likert scale
 8. Whether participant is willing to recommend the treatment to a friend
 9. Surgical intervention (hysterectomy, endometrial ablation and other gynaecological surgery)
 10. Adherence to trial treatments and reasons for changing treatment, as reported by the participant
 11. 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
 12. Clinical measurements via pelvic ultrasound: uterine volume, evidence of adenomyosis, presence of fibroids, largest fibroid volume, endometrial thickness, endometrial appearance (regular/irregular), evidence of ovarian cysts
 13. Clinical measurement via endometrial biopsy: primary diagnosis (normal/benign/hyperplasia/malignant) and further sub-diagnoses if non-normal
 14. Clinical measurement via blood samples: liver function (including alanine transaminase (ALT) and aspartate aminotransferase (AST) and other tests according to local protocols) serum haemoglobin and oestradiol levels
- Functional Outcomes
15. Impact on endometrial tissue architecture including regulation of the vascular compartment
 16. Impact on endometrial steroid responsiveness, proliferation, survival and inflammatory

processes

17. Expression of genes implicated in pre-malignant change including tumour suppressors
18. Effects on uterine/ fibroid structure and vascularity as determined by MRI-DCE and high resolution structural MRI

Previous secondary outcome measures:

1. Menstrual bleeding will be captured by validated Pictorial Blood Loss Assessment Chart (PBAC). 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
2. Uterine Fibroid Symptom and Quality of Life (UFS-QoL) instrument, which contains a health related quality of life (HRQoL) domain and a symptom domain. This instrument will be only given to women diagnosed with fibroids
3. Sexual Activity Questionnaire, 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
4. 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
5. Adherence to trial treatments, as reported by the participant
6. 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
7. Clinical measurements to assess safety and efficacy will include serum haemoglobin as appropriate, oestradiol, pelvic ultrasound (endometrial appearance; fibroid volume) and endometrial biopsies (reported according to pre-agreed criteria by independent pathologists blinded to treatment allocations)
8. Impact on endometrial tissue architecture including regulation of the vascular compartment
9. Impact on endometrial steroid responsiveness, proliferation, survival and inflammatory processes
10. Expression of genes implicated in pre-malignant change including tumour suppressors
11. Effects on uterine/ fibroid structure and vascularity as determined by MRI-DCE and high-resolution structural MRI

Overall study start date

01/10/2014

Completion date

31/05/2021

Eligibility

Key inclusion criteria

Current inclusion criteria as of 21/05/2020:

1. Aged 18 years or over
2. Menstrual bleeding that she perceives to be heavy and troublesome
3. Willing to receive medical treatment with either UPA or LNG-IUS
4. Willing to undergo two pelvic ultrasounds
5. 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)

6. 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

7. Willing to use barrier contraception if allocated to UPA

8. Given written informed consent

9. 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

Previous inclusion criteria:

1. Females aged between 18 or over

2. Heavy menstrual bleeding at intervals of 25-42 days that she perceives to be heavy and troublesome

3. Willing to receive medical treatment with either UPA or LNGIUS

4. Willing to undergo two pelvic ultrasounds and at least one endometrial biopsy, but up to four if allocated to UPA

5. Willing to use barrier contraception if allocated to UPA

6. Given written informed consent

7. Willing to undergo one additional endometrial biopsy and at least three magnetic resonance imaging scan (if allocated to UPA, mechanistic substudy only)

Participant type(s)

Patient

Age group

Adult

Lower age limit

18 Years

Sex

Female

Target number of participants

Planned Sample Size: 220; UK Sample Size: 220; Description: The Mechanistic Sub-study is carried out only at the Royal Infirmary of Edinburgh and will require a sample size of approximately 20 participants. Added 21/05/2020: As a consequence of the urgent safety measure relating to UPA (12-Feb-2018) we will aim to recruit enough women to ensure our primary analysis population is unaffected by enforced non-compliance with UPA or knowledge of the issues around UPA. This means we will now need to recruit 302 women in total into the study in total, with a target of 172 participants used in the primary analysis as per the original sample size target.

Total final enrolment

236

Key exclusion criteria

Current exclusion criteria as of 21/05/2020:

1. Post-menopausal

2. A >14 week fibroid uterus and/or cavity length >11 cm confirmed by ultrasound scan

3. Submucosal fibroids >2cm diameter confirmed by ultrasound scan

4. Contraindications to UPA or LNG-IUS

5. Intention to continue current use of Cytochrome P450 (CYP3A4) inhibitors
6. Intention to continue current use of Cytochrome P450 (CYP3A4) inducers (e.g. Phenytoin, carbamazepine, rifampicin, St John's Wort)
7. Intention to continue current use of P-glycoprotein substrates (e.g. digoxin)
8. A past, current or suspected diagnosis of endometrial hyperplasia or neoplasia
9. History of liver problems
10. Exclusion from the trial or initiating a new course of UPA if Alanine transaminase (ALT) or aspartate aminotransferase (AST) more than 2-times the upper limit of normal (ULN)
11. Epilepsy managed with carbamazepine, phenytoin
12. Significant renal impairment
13. Pregnant
14. Current plans to become pregnant within 12 months
15. Currently breastfeeding
16. Severe asthma that is not sufficiently controlled by oral glucocorticoids
17. Past or current known history of with uterine, cervical, ovarian or breast cancer.
18. Current use of progestagen-releasing intrauterine device (except if allocated within UCON)
19. Intention to continue regular use of Mefenamic acid
20. Intention to continue regular use of Tranexamic acid
21. Intention to continue regular use of GnRH analogues
22. Intention to continue regular use of Progestagen-only contraceptive
23. Intention to continue regular use of any combined oral contraceptive pills
24. Intention to continue regular use of hormonal replacement therapy

Previous exclusion criteria:

1. A >14 week fibroid uterus and/or cavity length >11 cm confirmed by ultrasound scan
2. Submucosal fibroids >2cm diameter confirmed by ultrasound scan
3. Contraindications to UPA or LNGIUS
4. Current use of Cytochrome P450 (CYP3A4) inhibitors
5. Current use of Cytochrome P450 (CYP3A4) inducers
6. Current use of Pglycoprotein substrate (e.g. digoxin)
7. A past, current or suspected diagnosis of endometrial hyperplasia or endometrial neoplasia
8. Severe hepatic impairment
9. Suffer with epilepsy managed with carbamazepine, phenytoin
10. Significant renal impairment
11. Pregnant
12. Current plans to become pregnant within 12 months
13. Currently breastfeeding
14. Severe asthma that is not sufficiently controlled by oral glucocorticoidssteroids
15. Suffer with uterine, cervical, ovarian or breast cancer
16. Receiving Pglycoprotein substrates
17. Current use of progestagen releasing intrauterine device (except if allocated within UCON)
18. Continued regular use of Mefenamic acid
19. Continued regular use of Tranexamic acid
20. Continued regular use of GnRH analogues
21. Continued regular use of Progestagen only contraceptive
22. Continued regular use of any combined oral contraceptive pills

Date of first enrolment

01/04/2015

Date of final enrolment

28/02/2020

Locations

Countries of recruitment

England

Scotland

United Kingdom

Wales

Study participating centre

Royal Infirmary of Edinburgh (lead site)

51 Little France Drive

Edinburgh

United Kingdom

EH16 4SA

Study participating centre

Glasgow Royal Infirmary

84 Castle Street

Glasgow

United Kingdom

G4 0SF

Study participating centre

Liverpool Women's Hospital

Crown Street

Liverpool

United Kingdom

L8 7SS

Study participating centre

Aberdeen Royal Infirmary

Foresterhill

Aberdeen

United Kingdom

AB25 2ZN

Study participating centre
Birmingham Women's Hospital
Mindelsohn Way
Birmingham
United Kingdom
B15 2TG

Study participating centre
Royal Blackburn Teaching Hospital
East Lancashire Hospitals NHS Trust
Haslingden Rd
Blackburn
United Kingdom
BB2 3HH

Study participating centre
Pennine Acute Hospitals Trust
Oldham
United Kingdom
M8 5RB

Study participating centre
Cwm Taf University Health Board
Royal Glamorgan Hospital
Ynysmaerdy
Llantrisant
Pontypridd
United Kingdom
CF72 8XR

Study participating centre
Aneurin Bevan University Health Board
Llanfrechfa Grange Hospital
Llanfrechfa
Cwmbran
United Kingdom
NP44 8YN

Study participating centre
NHS Ayrshire and Arran
Kilmarnock

United Kingdom
KA2 0BE

Study participating centre
Betsi Cadwaladr University Health Board
Bangor
United Kingdom
LL13 7TD

Sponsor information

Organisation
NHS Lothian

Sponsor details
ACCORD
The Queens Medical Research Institute
47 Little France Crescent
Edinburgh
Scotland
United Kingdom
EH16 4TJ

Sponsor type
Hospital/treatment centre

ROR
<https://ror.org/03q82t418>

Funder(s)

Funder type
Government

Funder Name
National Institute for Health Research

Alternative Name(s)
National Institute for Health Research, NIHR Research, NIHRresearch, NIHR - National Institute for Health Research, NIHR (The National Institute for Health and Care Research), NIHR

Funding Body Type

Government organisation

Funding Body Subtype

National government

Location

United Kingdom

Results and Publications

Publication and dissemination plan

The final report will be written in accordance with funder (NIHR EME) guidelines and published via NIHR.

Intention to publish date

30/03/2023

Individual participant data (IPD) sharing plan

Requests for data generated during the UCON study will be considered by the University of Birmingham Clinical Trials Unit (BCTU). Data will typically be available 6 months after the primary publication. Only scientifically sound proposals from appropriately qualified Research Groups will be considered for data sharing. The request will be reviewed by the BCTU Data Sharing Committee in discussion with the CI and, where appropriate (or in absence of the CI) any of the following: the Trial Sponsor, the relevant Trial Management Group (TMG), and independent TSC. Requests can be made to BCTU-Info@adf.bham.ac.uk

A formal Data Sharing Agreement (DSA) may be required between respective organisations once the release of the data is approved and before data can be released. Data will be fully de-identified (anonymised) unless the DSA covers the transfer of participant-identifiable information. Any data transfer will use a secure and encrypted method.

IPD sharing plan summary

Available on request

Study outputs

| Output type | Details | Date created | Date added | Peer reviewed? | Patient-facing? |
|--------------------------------------|-------------|--------------|------------|----------------|-----------------|
| Protocol file | version 7.0 | 23/03/2020 | 06/02/2023 | No | No |
| Results article | results | 18/05/2023 | 31/05/2023 | Yes | No |
| Other publications | | 22/05/2023 | 12/06/2023 | Yes | No |
| HRA research summary | | | 28/06/2023 | No | No |
| Results article | | 01/10/2023 | 23/04/2025 | Yes | No |