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Ulipristal acetate versus conventional management of heavy menstrual bleeding

Submission date
25/03/2015

Recruitment status
No longer recruiting

Registration date
25/03/2015

Overall study status
Completed

Last Edited
23/04/2025

Condition category
Urological and Genital Diseases

[X] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[X] Results
[_] 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 intone 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 intone 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

Contact information

Type(s)
Scientific

Contact name
Prof Hilary OD Critchley

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Additional identifiers

Clinical Trials Information System (CTIS)
2014-003408-65

Protocol serial number
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 themechanism 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

Primary study design
Interventional

Study design
Randomised; Interventional; Design type: Treatment

Study type(s)
Treatment

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(s)

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.

Key secondary outcome(s)

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 asparate 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

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

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 Years

Sex
Female

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
United Kingdom

England

Scotland

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

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

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?
Results article	results	18/05/2023	31/05/2023	Yes	No
Results article		01/10/2023	23/04/2025	Yes	No
HRA research summary			28/06/2023	No	No
Other publications		22/05/2023	12/06/2023	Yes	No

Protocol file	version 7.0	23/03/2020	06/02/2023	No	No
Study website	Study website	11/11/2025	11/11/2025	No	Yes