Clinical trial results:
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)

Summary

EudraCT number	2014-003408-65
Trial protocol	GB
Global end of trial date	30 June 2022

Results information

Result version number	v1 (current)
This version publication date	22 February 2023
First version publication date	22 February 2023

Trial information

Trial identification

Sponsor protocol code	UCON

Additional study identifiers

ISRCTN number	ISRCTN20426843
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	2014-003408-65: EudraCT

Notes:

Sponsors

Sponsor organisation name	University of Edinburgh and NHS Lothian
Sponsor organisation address	ACCORD, Queen's Medical Research Institute 47 Little France Crescent, Edinburgh, United Kingdom, EH16 4TJ
Public contact	Professor Hilary Critchley, University of Edinburgh, +44 1312426858, hilary.critchley@ed.ac.uk
Scientific contact	Professor Hilary Critchley, University of Edinburgh, +44 1312426858, hilary.critchley@ed.ac.uk

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	17 June 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	17 June 2022
Global end of trial reached?	Yes
Global end of trial date	30 June 2022
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Primary objective: to determine if UPA is more effective at reducing the burden of HMB symptoms than LNG-IUS after 12 months of treatment.

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.
Collect data on liver function in women taking UPA, once safety concerns were raised

Protection of trial subjects:

We ensure that all staff are GCP trained and will only grant access to allow staff at site to become involved in the trial if their GCP is in date. It is imperative that all investigators and staff at the sites have a thorough understanding of anticipated adverse events and the reporting process of these events as it is their responsibility to notify adverse events and SAE's to the Trial Office and for the Sponsor, or designated delegate, to report to the regulatory authority and ethics committee. The patient Information Sheet contained the details of the Patient Advice and Liaison Service (PALS) for the individual sites.

An Urgent Safety Measure(USM) was put in place following a drug alert for Ulipristal Acetate (UPA) issued on 13 March 2020 by the European Medicine Agency.
The following steps were put in place inline with advice from the competent authority:
1. Trial recruitment was suspended. No further participants were recruited to the UCON trial.
2. Participants who were on a 4 week stopping period between cycles, were advised not to resume UPA.
3. Any current or recent users of UPA presenting with signs or symptoms suggestive of liver injury (e.g. nausea, vomiting, malaise, right hypochondrial pain, anorexia, asthenia, jaundice) transaminase level's were checked.
4. Participants who stopped treatment remained on the trial and followed up as per the trial protocol.

Those allocated UPA were allowed to complete their current course of UPA treatment but not commence any further outstanding courses. In August 2018 the halt on UPA prescribing was lifted and recruitment to UCON resumed in October 2018 with additional safety measures in place. In March 2020 the EMA temporarily suspended use of UPA a second time due to ongoing concerns regarding hepatotoxicity and a further USM was issued. All treatment courses of UPA were immediately stopped. In view of the second USM the investigators, in discussion with Funder, chose premature closure of recruitment.

Background therapy: -

Evidence for comparator:

After eligibility had been established, baseline questionnaires completed, and once written informed consent had been obtained, the women were randomised into the trial.
A minimisation procedure using a computer based algorithm was used to avoid chance imbalances in treatment allocation and the following potentially important variables:
Age: ≤35yrs or >35yrs, BMI: ≤25 kg/m2 or >25 kg/m2, 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, a random factor within the algorithm in which for a proportion of the allocations (1 in 5) true randomisation was implemented rather than by using the minimised allocation.
Participants were randomised individually into the UCON trial in an equal ratio to either ulipristal acetate (UPA) or levonorgestrel releasing intrauterine system (LNG-IUS).

Actual start date of recruitment	01 March 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 236
Worldwide total number of subjects	236
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	236
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

UCON participants were recruited from gynaecology outpatient departments in ten NHS participating sites across the UK.

Pre-assignment

Screening details:

At the screening visit, a transvaginal and/or abdominal ultrasound scan was conducted and an endometrial biopsy taken. Blood samples (haemoglobin, serum oestradiol, with addition of liver function tests from 20th March 2018), were taken, clinical history was elicited, and a menstrual blood loss diary was provided to the participant.

Period 1

Period 1 title	Baseline
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Ulipristal acetate (UPA)

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Ulipristal acetate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

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. Any women randomised into the trial and allocated to UPA will be instructed to take the tablet in 3 courses according to the following cyclical (± 5 days) regime. Course 1 ON TREATMENT: One 5mg tablet of UPA to be taken daily for 12 weeks; OFF TREATMENT: UPA stopped for 4 weeks, when light vaginal bleeding may occur. Course 2 ON TREATMENT: One 5mg tablet of UPA to be taken daily for 12 weeks; OFF TREATMENT: UPA stopped for 4 weeks, when light vaginal bleeding may occur. Course 3 ON TREATMENT: One 5mg tablet of UPA to be taken daily for 12 weeks; OFF TREATMENT: UPA stopped for 4 weeks, when light vaginal bleeding may occur.

Arm title	LNG-IUS

Arm description:

Levonorgestrel-releasing intra-uterine system, retained for up to 5 years (depending on the product and manufacturer).

Arm type	Active comparator
Investigational medicinal product name	Levonorgestrel-releasing intrauterine system (LNG-IUS)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Intrauterine delivery system
Routes of administration	Vaginal use

Dosage and administration details:

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 approximately every three or five years, depending on the product.

Number of subjects in period 1	Ulipristal acetate (UPA)	LNG-IUS
Started	118	118
Completed	118	118

Period 2

Period 2 title	12 months
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Ulipristal acetate (UPA)

Arm description:

UPA is provided as a 5mg tablet. The trade name for UPA in the European Union is Esmya™ for treatment of uterine fibroids.

Arm type	Experimental
Investigational medicinal product name	Ulipristal acetate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

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. Any women randomised into the trial and allocated to UPA will be instructed to take the tablet in 3 courses according to the following cyclical (± 5 days) regime. Course 1 ON TREATMENT: One 5mg tablet of UPA to be taken daily for 12 weeks; OFF TREATMENT: UPA stopped for 4 weeks, when light vaginal bleeding may occur. Course 2 ON TREATMENT: One 5mg tablet of UPA to be taken daily for 12 weeks; OFF TREATMENT: UPA stopped for 4 weeks, when light vaginal bleeding may occur. Course 3 ON TREATMENT: One 5mg tablet of UPA to be taken daily for 12 weeks; OFF TREATMENT: UPA stopped for 4 weeks, when light vaginal bleeding may occur.

Arm title	LNG-IUS

Arm description:

Levonorgestrel-releasing intra-uterine system, retained for up to 5 years (depending on the product and manufacturer).

Arm type	Active comparator
Investigational medicinal product name	Levonorgestrel-releasing intrauterine system (LNG-IUS)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Intrauterine delivery system
Routes of administration	Vaginal use

Dosage and administration details:

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 approximately every three or five years, depending on the product.

Number of subjects in period 2[1]	Ulipristal acetate (UPA)	LNG-IUS
Started	89	79
3 months	79	65
6 months	62	53
Completed	53	50
Not completed	36	29
Completed after USM	36	29

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Number in analysis population not the same as those randomised due to USM; only those participants completed assessment prior to USM were included.

Baseline characteristics

Reporting groups	
Reporting group title	Ulipristal acetate (UPA)
Reporting group description: -	
Reporting group title	LNG-IUS
Reporting group description:	
Levonorgestrel-releasing intra-uterine system, retained for up to 5 years (depending on the product and manufacturer).	

Reporting group values	Ulipristal acetate (UPA)	LNG-IUS	Total
Number of subjects	118	118	236
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
35 and under	15	15	30
Over 35	103	103	206
Age continuous Units: years			
arithmetic mean	42.7	42.4	
standard deviation	± 7.0	± 6.9	-
Gender categorical Units: Subjects			
Female	118	118	236
Male	0	0	0
BMI Units: Subjects			
<= 25kg/m2	28	28	56
>25 kg/m2	90	90	180
Duration of symptoms Units: Subjects			
<1 year	16	12	28
>= 1 year	102	106	208
Fibroids Units: Subjects			
Fibroids > 2cm	31	27	58
Fibroids ≤ 2cm	12	11	23
No Fibroids	75	80	155
Number of Fibroids			

Figures based (denominator) on those that were identified as having fibroids on ultrasound			
Units: Subjects			
No fibroids	75	80	155
1 fibroid	23	21	44
2 fibroids	8	8	16
More than 2 fibroids	12	9	21
Agreement to enter sub-study Units: Subjects			
MRI Only	0	0	0
Biopsy Only	1	0	1
Neither/not applicable	95	96	191
Both MRI and Biopsy	22	22	44
Ethnicity Units: Subjects			
White	110	108	218
Mixed	2	1	3
Asian	4	6	10
Black	2	3	5
Other Ethnic Group	0	0	0
Not stated	0	0	0
Missing	0	0	0
BMI Units: kg/m2			
arithmetic mean	30.7	30.9	
standard deviation	± 7.0	± 7.1	-
Duration of Symptoms Units: month			
median	24	48	
inter-quartile range (Q1-Q3)	15 to 64	15 to 84	-

Subject analysis sets

Subject analysis set title	Population at 3 months: UPA
Subject analysis set type	Full analysis

Subject analysis set description:

Analysis population who returned a form at 3 months. Population includes those who completed assessments prior to USM.

Subject analysis set title	Population at 6 months: UPA
Subject analysis set type	Full analysis

Subject analysis set description:

Analysis population who returned a form at 6 months. Population includes those who completed assessments prior to USM.

Subject analysis set title	Population at 3 months: LNG-IUS
Subject analysis set type	Full analysis

Subject analysis set description:

Analysis population who returned a form at 3 months. Population includes those who completed assessments prior to USM.

Subject analysis set title	Population at 6 months: LNG-IUS
Subject analysis set type	Full analysis

Subject analysis set description:

Analysis population who returned a form at 6 months. Population includes those who completed assessments prior to USM.

Reporting group values	Population at 3 months: UPA	Population at 6 months: UPA	Population at 3 months: LNG-IUS
Number of subjects	79	62	65
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
35 and under	10	8	8
Over 35	69	54	57
Age continuous Units: years			
arithmetic mean			
standard deviation	±	±	±
Gender categorical Units: Subjects			
Female	79	62	65
Male	0	0	0
BMI Units: Subjects			
<= 25kg/m2			
>25 kg/m2			
Duration of symptoms Units: Subjects			
<1 year			
>= 1 year			
Fibroids Units: Subjects			
Fibroids > 2cm			
Fibroids ≤ 2cm			
No Fibroids			
Number of Fibroids			
Figures based (denominator) on those that were identified as having fibroids on ultrasound			
Units: Subjects			
No fibroids	50	39	41
1 fibroid	15	13	12
2 fibroids	6	4	4
More than 2 fibroids	8	6	8
Agreement to enter sub-study Units: Subjects			
MRI Only			
Biopsy Only			
Neither/not applicable			
Both MRI and Biopsy			

Ethnicity Units: Subjects			
White Mixed Asian Black Other Ethnic Group Not stated Missing			
BMI Units: kg/m2 arithmetic mean standard deviation	±	±	±
Duration of Symptoms Units: month median inter-quartile range (Q1-Q3)			

Reporting group values	Population at 6 months: LNG-IUS		
Number of subjects	53		
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over 35 and under Over 35	0 0 0 0 0 0 0 0 0 7 46		
Age continuous Units: years arithmetic mean standard deviation	±		
Gender categorical Units: Subjects			
Female Male	53 0		
BMI Units: Subjects			
<= 25kg/m2 >25 kg/m2			
Duration of symptoms Units: Subjects			
<1 year >= 1 year			
Fibroids			

Units: Subjects			
Fibroids > 2cm Fibroids ≤ 2cm No Fibroids			
Number of Fibroids			
Figures based (denominator) on those that were identified as having fibroids on ultrasound			
Units: Subjects			
No fibroids 1 fibroid 2 fibroids More than 2 fibroids	34 10 4 5		
Agreement to enter sub-study Units: Subjects			
MRI Only Biopsy Only Neither/not applicable Both MRI and Biopsy			
Ethnicity Units: Subjects			
White Mixed Asian Black Other Ethnic Group Not stated Missing			
BMI Units: kg/m2 arithmetic mean standard deviation	 ±		
Duration of Symptoms Units: month median inter-quartile range (Q1-Q3)			

End points

End points reporting groups

Reporting group title	Ulipristal acetate (UPA)
Reporting group description: -	
Reporting group title	LNG-IUS
Reporting group description:	
Levonorgestrel-releasing intra-uterine system, retained for up to 5 years (depending on the product and manufacturer).	
Reporting group title	Ulipristal acetate (UPA)
Reporting group description:	
UPA is provided as a 5mg tablet. The trade name for UPA in the European Union is Esmya™ for treatment of uterine fibroids.	
Reporting group title	LNG-IUS
Reporting group description:	
Levonorgestrel-releasing intra-uterine system, retained for up to 5 years (depending on the product and manufacturer).	
Subject analysis set title	Population at 3 months: UPA
Subject analysis set type	Full analysis
Subject analysis set description:	
Analysis population who returned a form at 3 months. Population includes those who completed assessments prior to USM.	
Subject analysis set title	Population at 6 months: UPA
Subject analysis set type	Full analysis
Subject analysis set description:	
Analysis population who returned a form at 6 months. Population includes those who completed assessments prior to USM.	
Subject analysis set title	Population at 3 months: LNG-IUS
Subject analysis set type	Full analysis
Subject analysis set description:	
Analysis population who returned a form at 3 months. Population includes those who completed assessments prior to USM.	
Subject analysis set title	Population at 6 months: LNG-IUS
Subject analysis set type	Full analysis
Subject analysis set description:	
Analysis population who returned a form at 6 months. Population includes those who completed assessments prior to USM.	

Primary: Menorrhagia Multi-Attribute Scale Scores at 12 months

End point title	Menorrhagia Multi-Attribute Scale Scores at 12 months
End point description:	
End point type	Primary
End point timeframe:	
Questionnaire completed at baseline, 3 months, 6 months and 12 months (primary end-point)	

End point values	Ulipristal acetate (UPA)	LNG-IUS		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	50		
Units: Participants				
≤ 50	12	6		
51-75	8	9		
76-99	12	12		
100	21	23		

Statistical analyses

Statistical analysis title	Primary Outcome: MMAS Category
Comparison groups	LNG-IUS v Ulipristal acetate (UPA)
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.12
Method	Chi-squared
Parameter estimate	Odds ratio (OR)
Point estimate	0.55
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.26
upper limit	1.17

Secondary: PBAC bleeding score at 12 months: amenorrhea

End point title	PBAC bleeding score at 12 months: amenorrhea
End point description:	
End point type	Secondary
End point timeframe:	
PBAC bleeding score at 12 months	

End point values	Ulipristal acetate (UPA)	LNG-IUS		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	40		
Units: Participants	18	10		

Statistical analyses

Statistical analysis title	PBAC Bleeding Score at 12 months
Comparison groups	Ulipristal acetate (UPA) v LNG-IUS
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	7.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.29
upper limit	22.2

Secondary: PBAC bleeding score at 12 months : Heavy bleeding

End point title	PBAC bleeding score at 12 months : Heavy bleeding
End point description:	
End point type	Secondary
End point timeframe:	
PBAC bleeding score at 12 months	

End point values	Ulipristal acetate (UPA)	LNG-IUS		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	40		
Units: Participants	5	12		

Statistical analyses

Statistical analysis title	Secondary Analysis: PBAC Bleeding Score = Heavy
Comparison groups	LNG-IUS v Ulipristal acetate (UPA)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	0.47
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.12
upper limit	1.79

Secondary: PBAC bleeding score at 12 months: Light Bleeding

End point title	PBAC bleeding score at 12 months: Light Bleeding

End point description:

End point type	Secondary

End point timeframe:

PBAC score at 12 months

End point values	Ulipristal acetate (UPA)	LNG-IUS		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	40		
Units: Participants	0	6		

Statistical analyses

No statistical analyses for this end point

Secondary: PBAC bleeding score at 12 months : Normal bleeding

End point title	PBAC bleeding score at 12 months : Normal bleeding

End point description:

End point type	Secondary

End point timeframe:

PBAC Score at 12 months

End point values	Ulipristal acetate (UPA)	LNG-IUS		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	40		
Units: Participants	5	12		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Menorrhagia Multi-Attribute Scale Scores at 3 months

End point title	Menorrhagia Multi-Attribute Scale Scores at 3 months

End point description:

End point type	Other pre-specified

End point timeframe:

Participants that returned a form at 3 months

End point values	Population at 3 months: UPA	Population at 3 months: LNG-IUS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	79	65		
Units: Participants				
≤50	14	16		
51-75	12	20		
76-99	19	17		
100	34	12		

Statistical analyses

Statistical analysis title	MMAS Category at 3 months
Comparison groups	Population at 3 months: UPA v Population at 3 months: LNG-IUS
Number of subjects included in analysis	144
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	2.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.24
upper limit	3.96

Other pre-specified: Menorrhagia Multi-Attribute Scale Scores at 6 months

End point title	Menorrhagia Multi-Attribute Scale Scores at 6 months

End point description:

End point type	Other pre-specified

End point timeframe:

Participants that returned forms at 6 months

End point values	Population at 6 months: UPA	Population at 6 months: LNG-IUS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	62	53		
Units: Participants				
≤50	16	7		
51-75	12	13		
76-99	13	13		
100	21	20		

Statistical analyses

Statistical analysis title	MMAS Category at 6 months
Comparison groups	Population at 6 months: UPA v Population at 6 months: LNG-IUS
Number of subjects included in analysis	115
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	0.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.33
upper limit	1.24

Other pre-specified: PBAC bleeding score at 3 months: amenorrhea	
End point title	PBAC bleeding score at 3 months: amenorrhea
End point description:	

End point type	Other pre-specified
End point timeframe:	
Follow up completed at 3 months	

End point values	Population at 3 months: UPA	Population at 3 months: LNG-IUS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	55	64		
Units: Participants	31	3		

Statistical analyses

Statistical analysis title	PBAC Bleeding Score at 3 months
Comparison groups	Population at 3 months: UPA v Population at 3 months: LNG-IUS
Number of subjects included in analysis	119
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	29.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	7.37
upper limit	116

Other pre-specified: PBAC bleeding score at 3 months: Light Bleeding

End point title	PBAC bleeding score at 3 months: Light Bleeding
End point description:	
End point type	Other pre-specified
End point timeframe:	
Follow up at 3 months	

End point values	Population at 3 months: UPA	Population at 3 months: LNG-IUS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	55	64		
Units: Participants	6	8		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: PBAC bleeding score at 3 months : Normal bleeding

End point title	PBAC bleeding score at 3 months : Normal bleeding
End point description:	
End point type	Other pre-specified
End point timeframe:	
Follow up at 3 months	

End point values	Population at 3 months: UPA	Population at 3 months: LNG-IUS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	55	64		
Units: Participants	4	32		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: PBAC bleeding score at 3 months : Heavy bleeding

End point title	PBAC bleeding score at 3 months : Heavy bleeding

End point description:

End point type	Other pre-specified

End point timeframe:

Follow up at 3 months

End point values	Population at 3 months: UPA	Population at 3 months: LNG-IUS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	55	64		
Units: Participants	14	53		

Statistical analyses

Statistical analysis title	PBAC Bleeding Score at 3 months
Comparison groups	Population at 3 months: UPA v Population at 3 months: LNG-IUS
Number of subjects included in analysis	119
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	0.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.27
upper limit	1.53

Other pre-specified: PBAC bleeding score at 6 months: amenorrhea	
End point title	PBAC bleeding score at 6 months: amenorrhea
End point description:	
End point type	Other pre-specified
End point timeframe:	
Follow up at 6 months	

End point values	Population at 6 months: UPA	Population at 6 months: LNG-IUS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	38	51		
Units: Participants	20	5		

Statistical analyses

Statistical analysis title	PBAC Bleeding Score at 6 months
Comparison groups	Population at 6 months: LNG-IUS v Population at 6 months: UPA
Number of subjects included in analysis	89
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	11.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.78
upper limit	36

Other pre-specified: PBAC bleeding score at 6 months : Light bleeding	
End point title	PBAC bleeding score at 6 months : Light bleeding
End point description:	
End point type	Other pre-specified
End point timeframe:	
Follow up at 6 months	

End point values	Population at 6 months: UPA	Population at 6 months: LNG-IUS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	38	51		
Units: Participants	3	10		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: PBAC bleeding score at 6 months : Normal bleeding

End point title	PBAC bleeding score at 6 months : Normal bleeding

End point description:

End point type	Other pre-specified

End point timeframe:

Follow up at 6 months

End point values	Population at 6 months: UPA	Population at 6 months: LNG-IUS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	38	51		
Units: Participants	10	29		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: PBAC bleeding score at 6 months : Heavy bleeding

End point title	PBAC bleeding score at 6 months : Heavy bleeding

End point description:

End point type	Other pre-specified

End point timeframe:

Follow up at 6 months

End point values	Population at 6 months: UPA	Population at 6 months: LNG-IUS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	38	51		
Units: Participants	5	7		

Statistical analyses

Statistical analysis title	PBAC Bleeding Score at 6 months
Comparison groups	Population at 6 months: UPA v Population at 6 months: LNG-IUS
Number of subjects included in analysis	89
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	0.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.23
upper limit	2.9

Other pre-specified: Total number of participants experiencing an SAE

End point title	Total number of participants experiencing an SAE
End point description:	
End point type	Other pre-specified
End point timeframe: SAEs reported to 12 months	

End point values	Ulipristal acetate (UPA)	LNG-IUS		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	118	118		
Units: Participants	6	5		

Statistical analyses

Statistical analysis title	Total number of participants experiencing an SAE
Comparison groups	Ulipristal acetate (UPA) v LNG-IUS

Number of subjects included in analysis	236
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.76
Method	Chi-squared

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were checked for at each follow up up to and including 12 months post randomisation

Adverse event reporting additional description:

There was one SUSAR in the UPA group (1/118, 1%), development of an acute hepatitis during the final course of UPA. However, the strong family history of autoimmune hepatitis led to her hepatology clinicians to conclude that this was the likely aetiology, and liver biopsy demonstrated widespread lymphoplastic hepatitis.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.1

Reporting groups

Reporting group title	Ulipristal acetate (UPA)
Reporting group description: -	
Reporting group title	LNG-IUS

Reporting group description:

Levonorgestrel-releasing intra-uterine system, retained for up to 5 years (depending on the product and manufacturer).

Serious adverse events	Ulipristal acetate (UPA)	LNG-IUS	
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 118 (5.08%)	5 / 118 (4.24%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
General disorders and administration site conditions			
Ureteric obstruction	Additional description: Ureteric obstruction AND Benign musculoskeletal and connective tissue neoplasms		
subjects affected / exposed	0 / 118 (0.00%)	1 / 118 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Uterine disorder	Additional description: Abnormal biopsy result post Esmya treatment; endometrial mass expelled		
subjects affected / exposed	2 / 118 (1.69%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast neoplasm	Additional description: Left breast cancer: Breast neoplasms unspecified malignancy AND Breast neoplasm removal		

subjects affected / exposed	1 / 118 (0.85%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fallopian tube operation	Additional description: Elective prophylactic surgery		
subjects affected / exposed	0 / 118 (0.00%)	1 / 118 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Heavy menstrual bleeding	Additional description: Increased menstrual bleeding and pain		
subjects affected / exposed	0 / 118 (0.00%)	1 / 118 (0.85%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystectomy			
subjects affected / exposed	1 / 118 (0.85%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Diarrhoea	Additional description: Background diarrhoea. Normal investigations including colonoscopy with biopsies 2011. Marked increased in frequency of diarrhoea 12/9/16. No associated symptoms. Mildly raised inflammatory markers: GP had referred to GI outpatients.		
subjects affected / exposed	1 / 118 (0.85%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Hip surgery	Additional description: Elective admission to hospital for total hip replacement		
subjects affected / exposed	1 / 118 (0.85%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Connective tissue neoplasm	Additional description: Removal of cervical fibroid		
subjects affected / exposed	0 / 118 (0.00%)	1 / 118 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sesamoidectomy	Additional description: Elective day surgery admission for removal of sesamoid bone		

subjects affected / exposed	0 / 118 (0.00%)	1 / 118 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Ulipristal acetate (UPA)	LNG-IUS	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 118 (12.71%)	7 / 118 (5.93%)	
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 118 (0.85%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Alopecia			
subjects affected / exposed	1 / 118 (0.85%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Anxiety			
subjects affected / exposed	2 / 118 (1.69%)	0 / 118 (0.00%)	
occurrences (all)	2	0	
Asthenia			
subjects affected / exposed	1 / 118 (0.85%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Dizziness			
subjects affected / exposed	2 / 118 (1.69%)	0 / 118 (0.00%)	
occurrences (all)	2	0	
General symptom			
subjects affected / exposed	0 / 118 (0.00%)	1 / 118 (0.85%)	
occurrences (all)	0	1	
Nausea	Additional description: Nausea and vomiting symptoms		
subjects affected / exposed	5 / 118 (4.24%)	0 / 118 (0.00%)	
occurrences (all)	5	0	
Blood and lymphatic system disorders			
Anaemia			

subjects affected / exposed	0 / 118 (0.00%)	1 / 118 (0.85%)	
occurrences (all)	0	1	
Platelet count			
subjects affected / exposed	0 / 118 (0.00%)	1 / 118 (0.85%)	
occurrences (all)	0	1	
Ear and labyrinth disorders			
Ear infection			
subjects affected / exposed	1 / 118 (0.85%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Gastrointestinal pain	Additional description: Gastrointestinal and abdominal pains		
subjects affected / exposed	3 / 118 (2.54%)	1 / 118 (0.85%)	
occurrences (all)	3	1	
Gastrointestinal pathogen panel	Additional description: Gastrointestinal and abdominal pains, chemistry analysis		
subjects affected / exposed	1 / 118 (0.85%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Reproductive system and breast disorders			
Menopausal symptoms			
subjects affected / exposed	1 / 118 (0.85%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Haemorrhage			
subjects affected / exposed	1 / 118 (0.85%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Reproductive tract disorder	Additional description: Reproductive tract signs and symptoms		
subjects affected / exposed	0 / 118 (0.00%)	2 / 118 (1.69%)	
occurrences (all)	0	2	
Vulvovaginal disorder	Additional description: Vulvovaginal signs and symptoms		
subjects affected / exposed	0 / 118 (0.00%)	2 / 118 (1.69%)	
occurrences (all)	0	2	
Respiratory, thoracic and mediastinal disorders			
Bronchospasm			
subjects affected / exposed	1 / 118 (0.85%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Coronavirus infection			
subjects affected / exposed	1 / 118 (0.85%)	0 / 118 (0.00%)	
occurrences (all)	1	0	

Upper respiratory tract infection			
subjects affected / exposed	4 / 118 (3.39%)	1 / 118 (0.85%)	
occurrences (all)	4	1	
Hepatobiliary disorders			
General symptom			
subjects affected / exposed	1 / 118 (0.85%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	1 / 118 (0.85%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Ecchymosis	Additional description: Bruising, Ecchymosis and purpura		
subjects affected / exposed	1 / 118 (0.85%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Soft tissue infection	Additional description: Oral soft tissue infection		
subjects affected / exposed	1 / 118 (0.85%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Bladder disorder			
subjects affected / exposed	3 / 118 (2.54%)	1 / 118 (0.85%)	
occurrences (all)	3	1	
Musculoskeletal and connective tissue disorders			
Musculoskeletal discomfort	Additional description: Musculoskeletal and connective tissue pain and discomfort		
subjects affected / exposed	5 / 118 (4.24%)	0 / 118 (0.00%)	
occurrences (all)	5	0	
Infections and infestations			
Helicobacter infection			
subjects affected / exposed	0 / 118 (0.00%)	1 / 118 (0.85%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 June 2015	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.
25 January 2016	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 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.
26 February 2018	Following an Urgent Safety Measure (12 February 2018) the following sections of the protocol have been updated accordingly; list of abbreviations; 5.1 Identifying Participants; 5.1.1 Identification from GP databases; 5.1.1.1 Raising awareness of the trial through community pharmacies; 5.1.2 GP Referral to Secondary Care; 5.1.3 Gynaecology Clinic Patient Identification; 5.2 Consenting for eligibility; 5.3 Re-Consenting Participants Following the USM; 5.35.4 Confirmation of eligibility before randomisation/entry into the mechanistic study; 5.5 Ineligible and Non-Recruited participants; 5.6 Randomisation; 5.6.1 Randomisation Procedures; 5.6.2 Treatment Allocation; Figure 2; 5.6.5 Stopping of treatment or Withdrawal of Study Participants; 6.1.7 Dispensing and accountability; 6.2.1 UPA; 6.2.2 LNG-IUS; 6.3 Dose Changes; 6.5 Special and Warning and precautions for use for Ulipristal Acetate (UPA); 7.1 Study Assessment Overview; 7.2 Timing of Study Assessments; Figure 4; Table 1; 10 Adverse Events and Pharmacovigilance; Appendix 1. The following new sections have been added; Important Notice (page 2); 5.6.1 Change of Treatment following USM; 6.6.1 Liver Injury (unconfirmed adverse reaction currently under investigation); 8.1.1 Liver Function Test Results.

06 September 2018	All references recruitment suspension have been removed and implications for resumption of recruitment described. Addition of 'history of liver problems' , 'ALT/AST more than 2 times the upper limit of normal, '5.1.1 – Identification from GP Practices' and '5.1.1 – GP Referral to Secondary Care' clarified. Figure 1 updated to include liver function tests (LFTs). '5.2 Consenting and Screening for Eligibility' clarified inclusive of LFTs. Figure 2 and 3 updated to incorporate LFTs. '5.6.5 Stopping of treatment or Withdrawal of Study Participants' updated to include LFT criteria and withdrawal clarification. '6.2 Dose and Delivery of IMPS', '6.5 Special Warnings and Precaution for Use for Ulipristal Acetate' and '7.3 Outcome Collected at Study Assessments' – updated to reflect LFT regime. '10 Adverse Events and Pharmacovigilance' – clarified. '12.3.1 Good Clinical Practice' clarified. Trial schema updated to include LFTs.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
12 February 2018	In February 2018, the trial was subject to an urgent safety measures (USM) as a consequence of drug alerts issued by the European Medicines Agency (EMA) and MHRA following reports of serious liver injury in patients receiving UPA treatment. Recruitment of participants to UCON was suspended.	18 October 2018
18 March 2020	In March 2020, the trial was subject to a second USM as a consequence of drug alerts issued by the European Medicines Agency (EMA) and MHRA following reports of serious liver injury in patients receiving UPA treatment. The EMA temporarily suspended use of UPA for a second time, whilst a further safety review was undertaken. Trial recruitment was suspended and the trial eventually halted in April 2020.	-

Notes:

Limitations and caveats

None reported