



## Clinical trial results: PROgesterone Therapy for Endometrial Cancer prevention in obese women (PROTEC)

### Summary

EudraCT number	2014-005610-37
Trial protocol	GB
Global end of trial date	01 October 2017

### Results information

Result version number	v1 (current)
This version publication date	30 May 2020
First version publication date	30 May 2020

### Trial information

#### Trial identification

Sponsor protocol code	PROTEC1
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#### Additional study identifiers

ISRCTN number	ISRCTN40940943
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	REC reference: 15/EE/0063

Notes:

### Sponsors

Sponsor organisation name	Manchester University NHS Foundation Trust
Sponsor organisation address	29 Grafton Street, Manchester, United Kingdom, M13 9WU
Public contact	Dr Lynne Webster, Head of the Research Office, Manchester University NHS Foundation Trust, +44 0161 276 4125, research.sponsor@mft.nhs.uk
Scientific contact	Dr Lynne Webster, Head of the Research Office, Manchester University NHS Foundation Trust, +44 0161 276 4125, research.sponsor@mft.nhs.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	01 October 2017
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	01 October 2017
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

To determine whether the Mirena coil is effective at interrupting pathways in the womb associated with increased risk of developing cancer.

Protection of trial subjects:

Taking part in the study involved a gift of time from the patients. Appointment times were made by telephone in advance for the most convenient time for the patient where possible and reasonable travel expenses were reimbursed. There was a discussion of personal information in the medical history, however the doctors involved in this study were practicing clinicians in the NHS and all information were handled and stored according to the Data Protection Act 1998. Having blood taken may be uncomfortable or cause bruising. The staff taking the samples were trained in phlebotomy. Endometrial biopsies and insertion of the Mirena IUS may be uncomfortable or embarrassing for some women. There is a small risk of infection and rarely uterine perforation. Genital swabs were taken during the screening assessment to reduce the risk of infection. Senior clinicians with experience in these procedures performed these tasks in a suitable environment for internal examinations with a female chaperone available at request. Should any patient find the clinical procedures too painful they were to be abandoned. The patients were fully informed of the risks and the signs and symptoms of possible complications. In the event of any complications the study patients were to be referred to the on call gynaecology team at St Mary's if necessary. The Mirena IUS can cause irregular bleeding (spotting) in some women. If the participants found this unacceptable we would remove the Mirena IUS at any time on request. Some women may find it distressing to realise they are at increased risk of endometrial cancer because they have a high BMI. If we were unable to obtain a baseline endometrial sample to reassure a patient routine gynaecology practice advice was given on risk reducing behaviours and any concerning features of history were to be investigated outside the research study.

Background therapy:

None

Evidence for comparator:

There was no comparator used within this trial.

Actual start date of recruitment	17 June 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 35
Worldwide total number of subjects	35
EEA total number of subjects	35

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)	35
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

The green light to begin recruitment to the study was issued by the sponsor on 17/06/2015. Participants were recruited from the Sleep Apnoea Clinic at Salford Royal Hospital which is a tertiary center that takes referrals from across the North West. Recruitment closed 31/07/2017.

### Pre-assignment

Screening details:

Inclusion:

- 1) Women seen in the Sleep Apnoea Clinic at Salford Royal Hospital
- 2) BMI >40
- 3) Consent
- 4) Aged 18 or over
- 5) Normal up to date smear
- 6) Normal endometrial sample at screening

Exclusion:

- 1) Previous hysterectomy
- 2) LNGIUS or IUD in situ or in previous 6 months
- 3) Pregnant or breast feeding
- 4) Progestin IUS contradicted

### Period 1

Period 1 title	Enrolment
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

There was no placebo or control group within this trial and so it was not blinded.

### Arms

Arm title	Mirena 20micrograms/24hours intrauterine delivery system
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Arm description:

Patients will undergo the following procedures:

1. Medical history, height, weight, blood pressure, waist and hip measurements
2. Telephone calls for menstrual history and adverse events
3. Questionnaire including MBL chart
4. Venepuncture 40mls blood for safety and trial bloods
5. Venepuncture 30mls blood for trialbloods
6. Mirena IUS insertion

Arm type	Experimental
Investigational medicinal product name	Levonorgestrel
Investigational medicinal product code	PL00010/0547
Other name	Mirena Intra Uterine System
Pharmaceutical forms	Vaginal delivery system
Routes of administration	Vaginal use

Dosage and administration details:

20 micrograms to be administered daily via a intrauterine delivery system for a duration of 9 months.

Number of subjects in period 1	Mirena 20micrograms/24hours intrauterine delivery system
Started	35
Completed	25
Not completed	10
Consent withdrawn by subject	4
Screen fail	6

## Period 2

Period 2 title	Baseline
Is this the baseline period?	Yes <sup>[1]</sup>
Allocation method	Not applicable
Blinding used	Not blinded

## Arms

<b>Arm title</b>	Mirena IUS
Arm description: -	
Arm type	Observational
Investigational medicinal product name	Levonorgestrel
Investigational medicinal product code	PL00010/0547
Other name	Mirena Intra Uterine System
Pharmaceutical forms	Vaginal delivery system
Routes of administration	Vaginal use

### Dosage and administration details:

20 micrograms to be administered daily via a intrauterine delivery system for a duration of 9 months.

### Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: There is an initial enrolment timepoint, when patients are identified and consented.

Number of subjects in period 2 <sup>[2]</sup>	Mirena IUS
Started	25
Completed	25

### Notes:

[2] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: 35 patients were enrolled into the study, but 6 were incorrectly enrolled and 4 withdraw their consent prior to collection of baseline data.

**Period 3**

Period 3 title	Followup - Implementation
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

**Arms**

<b>Arm title</b>	Mirena IUS - Implementation
Arm description: -	
Arm type	Observational
Investigational medicinal product name	Levonorgestrel
Investigational medicinal product code	PL00010/0547
Other name	Mirena Intra Uterine System
Pharmaceutical forms	Vaginal delivery system
Routes of administration	Vaginal use

Dosage and administration details:

20 micrograms to be administered daily via a intrauterine delivery system for a duration of 9 months.

<b>Number of subjects in period 3</b>	Mirena IUS - Implementation
Started	25
Completed	25

**Period 4**

Period 4 title	Followup - timepoint 2
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

**Arms**

<b>Arm title</b>	Mirena IUS - Timepoint 2
Arm description: -	
Arm type	Observational
Investigational medicinal product name	Levonorgestrel
Investigational medicinal product code	PL00010/0547
Other name	Mirena Intra Uterine System
Pharmaceutical forms	Vaginal delivery system
Routes of administration	Vaginal use

Dosage and administration details:

20 micrograms to be administered daily via a intrauterine delivery system for a duration of 9 months.

<b>Number of subjects in period 4</b>	Mirena IUS - Timepoint 2
Started	25
Completed	25

## Baseline characteristics

### Reporting groups

Reporting group title	Baseline
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Reporting group description: -

Reporting group values	Baseline	Total	
Number of subjects	25	25	
Age categorical			
Units: Subjects			
Adults (18-64 years)	25	25	
Age continuous			
At first biopsy			
Units: years			
arithmetic mean	53.6		
standard deviation	± 5.02	-	
Gender categorical			
Units: Subjects			
Female	25	25	
Ethnicity			
Units: Subjects			
Asian	1	1	
White	24	24	
Smoker			
Units: Subjects			
Ever	4	4	
Never	18	18	
Current	3	3	
Menopausal			
Units: Subjects			
Post	13	13	
Pre	12	12	
Cycle			
Units: Subjects			
Unknown	16	16	
Group I	5	5	
Group R	4	4	
Periods			
Units: Subjects			
Grp A	5	5	
Grp H	6	6	
Grp N	2	2	
Grp P	12	12	
IMB			
Units: Subjects			
Yes	1	1	
No	24	24	
PCB			

Units: Subjects			
Yes	0	0	
No	25	25	
PMB			
Units: Subjects			
Yes	2	2	
No	23	23	
HRT			
Units: Subjects			
Yes	3	3	
No	22	22	
Contraception/HRT			
Units: Subjects			
CC	1	1	
Ellest Duet	1	1	
Femiston	1	1	
Norethisterone	1	1	
Unknown	21	21	
Overdue smear			
Units: Subjects			
Yes	7	7	
No	18	18	
Smear result			
Units: Subjects			
Unknown	18	18	
No	7	7	
Comorbidities: Diabetes			
Units: Subjects			
Yes	10	10	
No	15	15	
Comorbidities: Subfertility			
Units: Subjects			
Yes	2	2	
No	23	23	
Comorbidities: Asthma/COPD			
Units: Subjects			
Yes	8	8	
No	17	17	
Comorbidities: Osteoarthritis/backpain			
Units: Subjects			
Yes	15	15	
No	10	10	
Comorbidities: Gallbladder/liver disease			
Units: Subjects			
Yes	5	5	
No	20	20	
Comorbidities: Depression/anxiety			
Units: Subjects			
Yes	8	8	
No	17	17	
Comorbidities: Hypertension			

Units: Subjects			
Yes	15	15	
No	10	10	
Comorbidities: GORD			
Units: Subjects			
Yes	4	4	
No	21	21	
Comorbidities: Thyroid disease			
Units: Subjects			
Yes	4	4	
No	21	21	
Comorbidities: Thromboembolic			
Units: Subjects			
Yes	3	3	
No	22	22	
Comorbidities: Hyperchol			
Units: Subjects			
Yes	5	5	
No	20	20	
Comorbidities: Sleep Apnea			
Units: Subjects			
Yes	9	9	
No	16	16	
Comorbidities: Cardiac Disease			
Units: Subjects			
Yes	2	2	
No	23	23	
Other comorbidities: Bone Marrow Transplant			
Units: Subjects			
Yes	1	1	
No	24	24	
Other comorbidities: Cellulitis			
Units: Subjects			
Yes	1	1	
No	24	24	
Other comorbidities: Crohns			
Units: Subjects			
Yes	1	1	
No	24	24	
Other comorbidities: Irritable bladder			
Units: Subjects			
Yes	1	1	
No	24	24	
Other comorbidities: Kidney			
Units: Subjects			
Yes	1	1	
No	24	24	
Other comorbidities: Migraine			
Units: Subjects			
Yes	2	2	

No	23	23	
Other comorbidities: Ovarian 1b Units: Subjects			
Yes	1	1	
No	24	24	
Over comorbidities: Ovarian cyst Units: Subjects			
Yes	1	1	
No	24	24	
Other comorbidities: Peripheral Neuropathy Units: Subjects			
Yes	1	1	
No	24	24	
Other comorbidities: Psychosis Units: Subjects			
Yes	1	1	
No	24	24	
Other comorbidities: Restless leg Units: Subjects			
Yes	1	1	
No	24	24	
Other comorbidities: Rhinitis, bells palsy Units: Subjects			
Yes	1	1	
No	24	24	
Menstrual cycle Units: Subjects			
Stage A	5	5	
Stage I	3	3	
Stage R	4	4	
Stage p	13	13	
Biopsy result Units: Subjects			
Result E	5	5	
Result N	20	20	
Parity Units: Subjects			
Zero	1	1	
One	6	6	
Two	10	10	
Three	2	2	
Four	3	3	
Five	1	1	
Six	0	0	
Seven	1	1	
Eight	1	1	
PCOS Units: Subjects			
Yes	6	6	
No	19	19	

Height Units: metres arithmetic mean standard deviation	1.6 ± 0.05	-	
Weight Units: kg arithmetic mean standard deviation	129.1 ± 19.16	-	
BMI Units: ratio (kg/msquared) arithmetic mean standard deviation	48.3 ± 6.27	-	
Waist circumference Units: cm arithmetic mean standard deviation	131.3 ± 13.60	-	
Hip circumference Units: cm arithmetic mean standard deviation	150.7 ± 13.96	-	
Waist Hip ratio Units: cm:cm arithmetic mean standard deviation	0.9 ± 0.07	-	
Dress Size Units: UK measurements arithmetic mean standard deviation	25.6 ± 4.37	-	
Dress size 10 years prior Units: UK dress size measurement arithmetic mean standard deviation	21.5 ± 4.76	-	
Day of cycle at baseline Units: Day median inter-quartile range (Q1-Q3)	16 11 to 37	-	
Duration of fast Units: Hours median inter-quartile range (Q1-Q3)	12 4 to 12	-	
HOMA Units: Index arithmetic mean standard deviation	12.5 ± 7.07	-	
Testosterone Units: nmol/L arithmetic mean standard deviation	7.1 ± 3.63	-	
Oestradiol Units: pg/ml arithmetic mean standard deviation	11.8 ± 6.55	-	

Progesterone Units: ng/mL median inter-quartile range (Q1-Q3)	1 1 to 4	-	
CRP Units: mg/L arithmetic mean standard deviation	9.0 ± 4.12	-	
Glucose Units: mmol/L arithmetic mean standard deviation	5.5 ± 0.82	-	
Insulin Units: mmol/L median inter-quartile range (Q1-Q3)	122 61 to 163	-	
FSH Units: IU/mL median inter-quartile range (Q1-Q3)	21.7 11.3 to 50.5	-	
LH Units: IU median inter-quartile range (Q1-Q3)	12.9 8.7 to 25.7	-	
LHFSHratio Units: Ratio arithmetic mean standard deviation	12.5 ± 7.07	-	
FAI Units: Index median inter-quartile range (Q1-Q3)	2.7 1.2 to 4.2	-	
HGB Units: g/dL median inter-quartile range (Q1-Q3)	35 29 to 51	-	
IGFBP Units: mg/L arithmetic mean standard deviation	99.7 ± 39.10	-	
Leptin Units: ng/dL median inter-quartile range (Q1-Q3)	70.3 56.4 to 90.7	-	
Adiponectin Units: µg/ml median inter-quartile range (Q1-Q3)	2.9 1.9 to 4.0	-	
HbA1c Units: mmol/mol arithmetic mean standard deviation	41.9 ± 8.20	-	

pAKTstrong Units: percentage median inter-quartile range (Q1-Q3)	0.0 0.0 to 4.5	-	
pAKTmoderate Units: percentage median inter-quartile range (Q1-Q3)	3.0 0.0 to 20.0	-	
pAKTweak Units: percentage median inter-quartile range (Q1-Q3)	75.0 45.0 to 99.0	-	
pAKTnegative Units: percentage median inter-quartile range (Q1-Q3)	0.0 0.0 to 35.0	-	
PRHScore Units: Score median inter-quartile range (Q1-Q3)	0.8 0.7 to 0.9	-	
PTENStrong Units: Percentage median inter-quartile range (Q1-Q3)	0.0 0.0 to 35.0	-	
PTENModerate Units: Percentage median inter-quartile range (Q1-Q3)	57.5 35.0 to 90.0	-	
PTENWeak Units: Percentage median inter-quartile range (Q1-Q3)	7.5 0.0 to 45.0	-	
ERgHScore Units: Score arithmetic mean standard deviation	0.8 $\pm 0.1$	-	
ERsHScore Units: Score arithmetic mean standard deviation	0.7 $\pm 0.1$	-	
Ki67 Total pos Units: Count median inter-quartile range (Q1-Q3)	321.5 30 to 407	-	
Ki67 Total neg Units: Count median inter-quartile range (Q1-Q3)	745.5 582 to 947	-	
Ki67 Pos Neg Ratio Units: Ratio median inter-quartile range (Q1-Q3)	0.335 0.027 to 0.685	-	

Ki67 Percent Pos			
Units: Percentage			
median	25.1		
inter-quartile range (Q1-Q3)	2.6 to 40.7	-	

## End points

### End points reporting groups

Reporting group title	Mirena 20micrograms/24hours intrauterine delivery system
Reporting group description: Patients will undergo the following procedures: 1. Medical history, height, weight, blood pressure, waist and hip measurements 2. Telephone calls for menstrual history and adverse events 3. Questionnaire including MBL chart 4. Venepuncture 40mls blood for safety and trial bloods 5. Venepuncture 30mls blood for trialbloods 6. Mirena IUS insertion	
Reporting group title	Mirena IUS
Reporting group description: -	
Reporting group title	Mirena IUS - Implementation
Reporting group description: -	
Reporting group title	Mirena IUS - Timepoint 2
Reporting group description: -	

### Primary: Ki67 Percentage Pos

End point title	Ki67 Percentage Pos <sup>[1]</sup>
End point description:	
End point type	Primary
End point timeframe:	
Followup	
Notes:	

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: This is a single arm exploratory study with small numbers looking at change in ki67 between baseline, implementation, and follow-up. A mixed effects regression model showed a significant difference at follow-up of around 15%. Potential confounders were not found to effect the outcome.

End point values	Mirena IUS - Implementation	Mirena IUS - Timepoint 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	25		
Units: Percentage				
median (inter-quartile range (Q1-Q3))	16.7 (10.8 to 30.9)	8.5 (5.3 to 16.5)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Ki67 Total pos

End point title	Ki67 Total pos
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End point description:

End point type	Secondary
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End point timeframe:

Follow-up

End point values	Mirena IUS - Implementatio n	Mirena IUS - Timepoint 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	25		
Units: Count				
median (inter-quartile range (Q1-Q3))	189.5 (91.5 to 395)	79 (48 to 158)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Ki67 Total neg

End point title	Ki67 Total neg
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End point description:

End point type	Secondary
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End point timeframe:

Followup

End point values	Mirena IUS - Implementatio n	Mirena IUS - Timepoint 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	25		
Units: Count				
median (inter-quartile range (Q1-Q3))	880 (673 to 1063)	945 (698 to 971)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Ki67 Pos Neg Ratio

End point title	Ki67 Pos Neg Ratio
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End point description:

End point type	Secondary
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End point timeframe:

Followup

End point values	Mirena IUS - Implementatio n	Mirena IUS - Timepoint 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	25		
Units: Ratio				
median (inter-quartile range (Q1-Q3))	0.201 (0.121 to 0.449)	0.093 (0.056 to 0.198)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Weight

End point title	Weight
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End point description:

End point type	Secondary
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End point timeframe:

Followup

End point values	Mirena IUS - Implementatio n	Mirena IUS - Timepoint 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	25		
Units: kg				
arithmetic mean (standard deviation)	128.3 (± 19.4)	126.7 (± 19.2)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: BMI

End point title	BMI
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End point description:

End point type	Secondary
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End point timeframe:

Followup

End point values	Mirena IUS - Implementatio n	Mirena IUS - Timepoint 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	25		
Units: ratio (kg/msquared)				
arithmetic mean (standard deviation)	48.0 (± 6.4)	47.5 (± 6.7)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Waist circumference

End point title	Waist circumference
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End point description:

End point type	Secondary
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End point timeframe:

Followup

End point values	Mirena IUS - Implementatio n	Mirena IUS - Timepoint 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	24		
Units: cm				
arithmetic mean (standard deviation)	130.8 (± 13.2)	128.1 (± 14.3)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Hip circumference

End point title	Hip circumference
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End point description:

End point type	Secondary
End point timeframe:	
Followup	

End point values	Mirena IUS - Implementatio n	Mirena IUS - Timepoint 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	24		
Units: cm				
arithmetic mean (standard deviation)	149.5 (± 13.7)	147.6 (± 14.2)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Waist hip ratio

End point title	Waist hip ratio
End point description:	
End point type	Secondary
End point timeframe:	
Followup	

End point values	Mirena IUS - Implementatio n	Mirena IUS - Timepoint 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	24		
Units: Ratio				
arithmetic mean (standard deviation)	0.88 (± 0.07)	0.87 (± 0.07)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: HOMA

End point title	HOMA
End point description:	
End point type	Secondary

End point timeframe:

Followup

End point values	Mirena IUS - Implementatio n	Mirena IUS - Timepoint 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	21		
Units: Index				
arithmetic mean (standard deviation)	28.0 ( $\pm$ 24.3)	33.8 ( $\pm$ 34.9)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Testosterone

End point title	Testosterone
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End point description:

End point type	Secondary
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End point timeframe:

Followup

End point values	Mirena IUS - Implementatio n	Mirena IUS - Timepoint 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	25		
Units: nmol/L				
arithmetic mean (standard deviation)	6.3 ( $\pm$ 3.4)	6.8 ( $\pm$ 3.7)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Oestradiol

End point title	Oestradiol
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End point description:

End point type	Secondary
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End point timeframe:

Followup

End point values	Mirena IUS - Implementatio n	Mirena IUS - Timepoint 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	25		
Units: pg/mL				
arithmetic mean (standard deviation)	9.7 ( $\pm$ 5.5)	10.1 ( $\pm$ 6.0)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Progesterone

End point title	Progesterone
End point description:	
End point type	Secondary
End point timeframe:	
Followup	

End point values	Mirena IUS - Implementatio n	Mirena IUS - Timepoint 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	25		
Units: ng/mL				
median (inter-quartile range (Q1-Q3))	1.0 (1.0 to 6.5)	1.0 (1.0 to 1.0)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: CRP

End point title	CRP
End point description:	
End point type	Secondary
End point timeframe:	
Followup	

End point values	Mirena IUS - Implementatio n	Mirena IUS - Timepoint 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	25		
Units: mg/L				
arithmetic mean (standard deviation)	6.2 ( $\pm$ 3.3)	7.3 ( $\pm$ 4.0)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Glucose

End point title	Glucose
End point description:	
End point type	Secondary
End point timeframe:	
Followup	

End point values	Mirena IUS - Implementatio n	Mirena IUS - Timepoint 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	24		
Units: mmol/L				
arithmetic mean (standard deviation)	5.5 ( $\pm$ 1.0)	5.5 ( $\pm$ 0.9)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Insulin

End point title	Insulin
End point description:	
End point type	Secondary
End point timeframe:	
Followup	

End point values	Mirena IUS - Implementation	Mirena IUS - Timepoint 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	24		
Units: mmol/L				
median (inter-quartile range (Q1-Q3))	89.5 (76 to 156)	79.5 (55.5 to 173)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: FSH

End point title	FSH
End point description:	
End point type	Secondary
End point timeframe:	
Followup	

End point values	Mirena IUS - Implementation	Mirena IUS - Timepoint 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	25		
Units: IU/mL				
median (inter-quartile range (Q1-Q3))	20.85 (8.8 to 43.6)	23.7 (13.3 to 53.5)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: LH

End point title	LH
End point description:	
End point type	Secondary
End point timeframe:	
Followup	

End point values	Mirena IUS - Implementatio n	Mirena IUS - Timepoint 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	24		
Units: IU				
median (inter-quartile range (Q1-Q3))	11.8 (5.4 to 26.5)	16.75 (9.95 to 38.45)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: LHFSHRatio

End point title	LHFSHRatio
End point description:	
End point type	Secondary
End point timeframe:	
Followup	

End point values	Mirena IUS - Implementatio n	Mirena IUS - Timepoint 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	24		
Units: Ratio				
arithmetic mean (standard deviation)	0.70 ( $\pm$ 0.27)	0.68 ( $\pm$ 0.17)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: FAI

End point title	FAI
End point description:	
End point type	Secondary
End point timeframe:	
Followup	

End point values	Mirena IUS - Implementatio n	Mirena IUS - Timepoint 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	24		
Units: Index				
median (inter-quartile range (Q1-Q3))	1.75 (0.9 to 3.6)	1.95 (1.25 to 3.85)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: HBG

End point title	HBG
End point description:	
End point type	Secondary
End point timeframe:	
Followup	

End point values	Mirena IUS - Implementatio n	Mirena IUS - Timepoint 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	25		
Units: g/dL				
median (inter-quartile range (Q1-Q3))	36 (27.5 to 61)	30 (27 to 56)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: IGFBP

End point title	IGFBP
End point description:	
End point type	Secondary
End point timeframe:	
Followup	

End point values	Mirena IUS - Implementatio n	Mirena IUS - Timepoint 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	16		
Units: mg/L				
arithmetic mean (standard deviation)	98.3 ( $\pm$ 49.6)	100.8 ( $\pm$ 35.3)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Leptin

End point title	Leptin
End point description:	
End point type	Secondary
End point timeframe:	
Secondary	

End point values	Mirena IUS - Implementatio n	Mirena IUS - Timepoint 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	24		
Units: ncpa.cpl				
median (inter-quartile range (Q1-Q3))	72.2 (54.8 to 96.4)	76.2 (62.0 to 97.7)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Adiponectin

End point title	Adiponectin
End point description:	
End point type	Secondary
End point timeframe:	
Followup	

End point values	Mirena IUS - Implementatio n	Mirena IUS - Timepoint 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	24		
Units: µg/ml				
median (inter-quartile range (Q1-Q3))	2.8 (2.0 to 3.8)	2.0 (1.6 to 3.3)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: HbA1c

End point title	HbA1c
End point description:	
End point type	Secondary
End point timeframe:	
Followup	

End point values	Mirena IUS - Implementatio n	Mirena IUS - Timepoint 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	23		
Units: mmol/mol				
arithmetic mean (standard deviation)	41.7 (± 9.3)	42.2 (± 9.5)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: IGF1

End point title	IGF1
End point description:	
End point type	Secondary
End point timeframe:	
Followup	

End point values	Mirena IUS - Implementatio n	Mirena IUS - Timepoint 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	24		
Units: ng/ml,				
arithmetic mean (standard deviation)	10.0 (± 5.2)	10.3 (± 5.7)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: pAKTstrong

End point title	pAKTstrong
End point description:	
End point type	Secondary
End point timeframe:	
Followup	

End point values	Mirena IUS - Implementatio n	Mirena IUS - Timepoint 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	20		
Units: Percentage				
median (inter-quartile range (Q1-Q3))	0 (0 to 1)	0 (0 to 0)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: pAKTmoderate

End point title	pAKTmoderate
End point description:	
End point type	Secondary
End point timeframe:	
Followup	

End point values	Mirena IUS - Implementatio n	Mirena IUS - Timepoint 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	21		
Units: Percentage				
median (inter-quartile range (Q1-Q3))	1 (0 to 9)	0 (0 to 5)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: pAKTnegative

End point title	pAKTnegative
End point description:	
End point type	Secondary
End point timeframe:	
Followup	

End point values	Mirena IUS - Implementatio n	Mirena IUS - Timepoint 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	22		
Units: Percentage				
median (inter-quartile range (Q1-Q3))	7.5 (0.5 to 39)	10 (4 to 40)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: pAKTweak

End point title	pAKTweak
End point description:	
End point type	Secondary
End point timeframe:	
Followup	

End point values	Mirena IUS - Implementatio n	Mirena IUS - Timepoint 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	24		
Units: Percentage				
median (inter-quartile range (Q1-Q3))	80 (52 to 98)	80 (60 to 97.5)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: PRHScore

End point title	PRHScore
End point description:	
End point type	Secondary
End point timeframe:	
Followup	

End point values	Mirena IUS - Implementatio n	Mirena IUS - Timepoint 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	23		
Units: Score				
median (inter-quartile range (Q1-Q3))	0.8889 (0.7778 to 0.9444)	0.4444 (0.3333 to 0.5556)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: PTENStrong

End point title	PTENStrong
End point description:	
End point type	Secondary
End point timeframe:	
Followup	

End point values	Mirena IUS - Implementatio n	Mirena IUS - Timepoint 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	25		
Units: Percentage				
median (inter-quartile range (Q1-Q3))	0 (0 to 30)	0 (0 to 5)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: PTENModerate

End point title	PTENModerate
End point description:	
End point type	Secondary
End point timeframe:	
Followup	

End point values	Mirena IUS - Implementatio n	Mirena IUS - Timepoint 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	25		
Units: Percentage				
median (inter-quartile range (Q1-Q3))	60 (40 to 95)	80 (50 to 100)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: PTENWeak

End point title	PTENWeak
End point description:	
End point type	Secondary
End point timeframe:	
Followup	

End point values	Mirena IUS - Implementatio n	Mirena IUS - Timepoint 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	25		
Units: Percentage				
median (inter-quartile range (Q1-Q3))	5 (0 to 35)	10 (0 to 35)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: ERgHScore

End point title	ERgHScore
End point description:	
End point type	Secondary
End point timeframe:	
Followup	

End point values	Mirena IUS - Implementatio n	Mirena IUS - Timepoint 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	22		
Units: Score				
arithmetic mean (standard deviation)	0.9 ( $\pm$ 0.1)	0.8 ( $\pm$ 0.1)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: ERsHScore

End point title	ERsHScore
End point description:	
End point type	Secondary
End point timeframe:	
Followup	

<b>End point values</b>	Mirena IUS - Implementatio n	Mirena IUS - Timepoint 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	21		
Units: Score				
arithmetic mean (standard deviation)	0.7 ( $\pm$ 0.1)	0.7 ( $\pm$ 0.1)		

### Statistical analyses

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

SAEs occurring within the duration of the study were collected and reported to the sponsor.

Adverse event reporting additional description:

AEs are recorded on a template AE log which were made available for review at monitoring visits. Any SAE will be reported by the Principal Investigator (including a completed SAE form) within 24 hours of first knowledge to the Sponsor.

Assessment type	Non-systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	1
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### Reporting groups

Reporting group title	Mirena 20micrograms/24hours intrauterine delivery system
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Reporting group description: -

Serious adverse events	Mirena 20micrograms/24hours intrauterine delivery system		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 35 (2.86%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Psychiatric disorders			
Patient swallowed (x60) co-codamo (500/30) tablets and went to bed. Woke the next morning, vomitted.			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Patient lay on the ground to die of dehydration for two nights			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

<b>Non-serious adverse events</b>	Mirena 20micrograms/24h urs intrauterine delivery system		
Total subjects affected by non-serious adverse events subjects affected / exposed	5 / 35 (14.29%)		
Pregnancy, puerperium and perinatal conditions Pelvic inflammatory disease subjects affected / exposed occurrences (all)	1 / 35 (2.86%)  1		
Blood and lymphatic system disorders Vasculitis subjects affected / exposed occurrences (all)	1 / 35 (2.86%)  1		
General disorders and administration site conditions Sciatica subjects affected / exposed occurrences (all)  Discomfort subjects affected / exposed occurrences (all)	1 / 35 (2.86%)  1  1 / 35 (2.86%)  1		
Infections and infestations Urinary Tract Infection subjects affected / exposed occurrences (all)	1 / 35 (2.86%)  1		

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 September 2015	<p>Substantial amendment 2: 1) The protocol is amended to allow recruitment of patients through the Sleep Apnoea or other service at Salford Royal or any gynaecology clinic at St Mary's Hospital Manchester or any patient who approaches the research team directly after hearing of the trial through "word of mouth", CRUK or clinical trials.gov or other clinical research website or publication. Notification of the participants involvement to their GP will remain compulsory for all trial participants.</p> <p>2) The use of an alternative (validated) questionnaire at the baseline/insertion of Mirena and follow up visits. After listening to the committee's original concerns regarding our questionnaire and feedback from our participants we wish to change the questionnaire to a more general health and wellbeing questionnaire and specific assessment on menstrual bleeding.</p> <p>3) The protocol is amended to allow contact of participants by their clinical team</p> <p>4) The protocol is amended to reflect that St Mary's Hospital is the only site where assessments will be performed</p> <p>5) The patient information sheet is amended to reflect the new questionnaire</p> <p>6) The consent form is amended to reflect the new version of the patient information sheet</p> <p>Received REC favourable opinion 20/10/2015.</p>
05 May 2016	<p>Substantial amendment 1: The protocol for this trial has been changed after ethics approval was granted at the request of the MHRA in their 'notice of grounds for nonacceptance' letter in response to our initial clinical trials application. The MHRA have requested that the protocol be amended to include the exclusion criteria of "postpartum endometritis, infected abortion during the past three months and recent trophoblastic disease while hCG levels remain elevated" before they approve the study. Received REC favourable opinion 22/05/2015.</p>

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported