



## Clinical trial results:

**A randomised controlled trial to investigate the effects of the use of pre-operative GnRH analogue and intra-operative mechanical tourniquet for myomectomy on surgical blood loss, future fertility and quality of life**

### Summary

EudraCT number	2010-019810-26
Trial protocol	GB
Global end of trial date	05 September 2019

### Results information

Result version number	v1 (current)
This version publication date	01 January 2021
First version publication date	01 January 2021
Summary attachment (see zip file)	Clinical Study report (Myomectomy paper Aug2020.pdf)

### Trial information

#### Trial identification

Sponsor protocol code	1968
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#### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

#### Sponsors

Sponsor organisation name	King's College Hospital NHS Foundation Trust
Sponsor organisation address	Denmark Hill, London, United Kingdom, SE5 9RS
Public contact	Mr Nitish Narvekar, Kings College Hospital Foundation NHS Trust, +44 020 3299 5390, nitish.narvekar@nhs.net
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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	18 September 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	05 September 2019
Global end of trial reached?	Yes
Global end of trial date	05 September 2019
Was the trial ended prematurely?	Yes

Notes:

## General information about the trial

Main objective of the trial:

To compare the clinical efficacy and cost-effectiveness of pre-operative use of GnRH analogues and intra-operative use of mechanical tourniquet in reducing intra-operative blood loss

Protection of trial subjects:

Patients will be able to withdraw their consent to taking part in the trial at any point. This will be discussed with them at every clinic visit. If they decide to withdraw as they are patients at Kings College Hospital they will continue to be followed up as per routine patient care. If they withdraw due to an adverse event then they will be followed up until the end of the trial or until the event is resolved (which ever is sooner).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 November 2012
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: 73
Worldwide total number of subjects	73
EEA total number of subjects	73

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)	73
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

A total of 73 subjects were recruited in total between April 2012 and April 2019 from King's College Hospital, London.

### Pre-assignment

Screening details:

Women were eligible if they were diagnosed with uterine fibroids on ultrasonography, opted for surgery and considered suitable for an open myomectomy by a consultant gynaecologist. Eligibility included women between ages 18-50 years, with a uterine size of over 14 weeks gestational equivalence and/or volume of over 600cm<sup>3</sup>.

### Pre-assignment period milestones

Number of subjects started	73
Number of subjects completed	43

### Pre-assignment subject non-completion reasons

Reason: Number of subjects	Consent withdrawn by subject: 30
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### Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

The study is not blinded however patients will be asked not to reveal to their allocation to their surgeon, in addition they will carry a card detailing their treatment allocation details. The allocation will be recorded in the notes but stored in an envelope to avoid the surgeon being un-blinded. Surgeons in Group A will be un-blinded to patient allocation. Surgeons in groups B and C will be blinded and will be unaware if the subject has had pre operative GnRH analogue.

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	A GnHR

Arm description:

Patients allocated to use of pre-operative GnRH analogues will be prescribed Prostag (Leuprorelin acetate depot injection, Takeda, UK) as a single dose of 3.75 mg by intramuscular or subcutaneous injection every 28 days, 3 months prior to surgery.

Arm type	Experimental
Investigational medicinal product name	prosrp SR DCS
Investigational medicinal product code	
Other name	LEUPRORELIN ACETATE
Pharmaceutical forms	Powder and solvent for suspension for injection in pre-filled syringe
Routes of administration	Intramuscular use, Subcutaneous use

Dosage and administration details:

Prostag (Leuprorelin acetate depot injection, Takeda, UK) as a single dose of 3.75 mg by intramuscular or subcutaneous injection every 28 days, 3 months prior to surgery. Total dose of 11.25mg over 3 months.

<b>Arm title</b>	B Tourniquet
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Arm description:

intra-operative mechanical tourniquet only

Arm type	surgical intervention
No investigational medicinal product assigned in this arm	
<b>Arm title</b>	C GnHR and Tourniquet
Arm description:	
Prostap (Leuporelin acetate depot injection, Takeda, UK) as a single dose of 3.75 mg by intramuscular or subcutaneous injection every 28 days, 3 months prior to surgery and intra-operative mechanical tourniquet	
Arm type	Experimental
Investigational medicinal product name	prosrp SR DCS
Investigational medicinal product code	
Other name	LEUPORELIN ACETATE
Pharmaceutical forms	Powder and solvent for suspension for injection in pre-filled syringe
Routes of administration	Intramuscular use, Subcutaneous use

Dosage and administration details:

Prostap (Leuporelin acetate depot injection, Takeda, UK) as a single dose of 3.75 mg by intramuscular or subcutaneous injection every 28 days, 3 months prior to surgery. Total dose of 11.25mg over 3 months.

<b>Number of subjects in period 1<sup>[1]</sup></b>	A GnHR	B Tourniquet	C GnHR and Tourniquet
Started	14	12	17
Completed	14	12	17

Notes:

[1] - 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: 30 withdrew or were lost to follow up prior to starting the intervention

## Baseline characteristics

### Reporting groups

Reporting group title	A GnHR
Reporting group description: Patients allocated to use of pre-operative GnRH analogues will be prescribed Prostag (Leuprorelin acetate depot injection, Takeda, UK) as a single dose of 3.75 mg by intramuscular or subcutaneous injection every 28 days, 3 months prior to surgery.	
Reporting group title	B Tourniquet
Reporting group description: intra-operative mechanical tourniquet only	
Reporting group title	C GnHR and Tourniquet
Reporting group description: Prostag (Leuprorelin acetate depot injection, Takeda, UK) as a single dose of 3.75 mg by intramuscular or subcutaneous injection every 28 days, 3 months prior to surgery and intra-operative mechanical tourniquet	

Reporting group values	A GnHR	B Tourniquet	C GnHR and Tourniquet
Number of subjects	14	12	17
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			
Age continuous Units: years			
arithmetic mean	40.8	39.8	41.1
standard deviation	± 4.7	± 5.1	± 4.6
Gender categorical Units: Subjects			
Female	14	12	17
Male	0	0	0
ethnicity Units: Subjects			
white	1	0	1
black	12	12	16
asian	1	0	0
Anaemia			
Hb<12g/L			
Units: Subjects			
Hb<12g/L	2	5	1
Hb>12g/L	12	7	16

Parity			
Units: Subjects			
No previous births	11	9	14
>= 1 birth	3	3	3
smoking status			
Units: Subjects			
smoker	1	0	2
non-smoker	13	12	15
BMI			
Units: kg/m2			
arithmetic mean	29	30.9	29.8
standard deviation	± 4.4	± 4	± 4.3

<b>Reporting group values</b>	Total		
Number of subjects	43		
Age categorical			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	0		
From 65-84 years	0		
85 years and over	0		
Age continuous			
Units: years			
arithmetic mean	-		
standard deviation			
Gender categorical			
Units: Subjects			
Female	43		
Male	0		
ethnicity			
Units: Subjects			
white	2		
black	40		
asian	1		
Anaemia			
Hb<12g/L			
Units: Subjects			
Hb<12g/L	8		
Hb>12g/L	35		
Parity			
Units: Subjects			
No previous births	34		
>= 1 birth	9		
smoking status			
Units: Subjects			

smoker	3		
non-smoker	40		

BMI			
Units: kg/m2			
arithmetic mean			
standard deviation	-		

## End points

### End points reporting groups

Reporting group title	A GnHR
Reporting group description: Patients allocated to use of pre-operative GnRH analogues will be prescribed Prostag (Leuprorelin acetate depot injection, Takeda, UK) as a single dose of 3.75 mg by intramuscular or subcutaneous injection every 28 days, 3 months prior to surgery.	
Reporting group title	B Tourniquet
Reporting group description: intra-operative mechanical tourniquet only	
Reporting group title	C GnHR and Tourniquet
Reporting group description: Prostag (Leuprorelin acetate depot injection, Takeda, UK) as a single dose of 3.75 mg by intramuscular or subcutaneous injection every 28 days, 3 months prior to surgery and intra-operative mechanical tourniquet	

### Primary: mean blood loss

End point title	mean blood loss <sup>[1]</sup>
End point description: Evaluation of Blood loss: Special drapes will be placed in the abdomen to collect blood during surgery. The collected blood will be suctioned continuously into a cell saver apparatus for measurement and auto-transfusion if appropriate. Blood absorbed by surgical swabs will be estimated using dry and swab weight differential measurement using the appropriate conversion factor. Blood collected in any post-operative drains, which are used per clinical need, will be measured to compute the total peri-operative blood loss.	
End point type	Primary
End point timeframe: In operative	
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: Please see linked summary report	

End point values	A GnHR	B Tourniquet	C GnHR and Tourniquet	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	14	12	17	
Units: ml				
arithmetic mean (standard deviation)	1210 (± 965)	458 (± 387)	406 (± 285)	

### Statistical analyses

No statistical analyses for this end point



## Adverse events

### Adverse events information<sup>[1]</sup>

Timeframe for reporting adverse events:

Participants in Group A (GnHR) & C (GnHR + tourniquet) were asked questions regarding any adverse events at their monthly visits 3 months pre-operation. All subjects were reviewed for AEs at their pre-admission visit and whilst inpatients.

Assessment type	Non-systematic
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### Dictionary used

Dictionary name	MedDRA
Dictionary version	23.1

### Reporting groups

Reporting group title	A GnHR
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Reporting group description:

Patients allocated to use of pre-operative GnRH analogues will be prescribed Prostag (Leuprorelin acetate depot injection, Takeda, UK) as a single dose of 3.75 mg by intramuscular or subcutaneous injection every 28 days, 3 months prior to surgery.

Reporting group title	B Tourniquet
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Reporting group description:

intra-operative mechanical tourniquet only

Reporting group title	C GnHR and Tourniquet
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Reporting group description:

Prostag (Leuprorelin acetate depot injection, Takeda, UK) as a single dose of 3.75 mg by intramuscular or subcutaneous injection every 28 days, 3 months prior to surgery and intra-operative mechanical tourniquet

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.

Justification: Any medical occurrences which occurred resulted in a prolonged hospital stay/additional hospital stay - and so these were all reported as an SAE.

Serious adverse events	A GnHR	B Tourniquet	C GnHR and Tourniquet
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 14 (7.14%)	1 / 12 (8.33%)	2 / 17 (11.76%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Haemoglobin decreased			
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	1 / 17 (5.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Sepsis			
subjects affected / exposed	1 / 14 (7.14%)	1 / 12 (8.33%)	0 / 17 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			

subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	1 / 17 (5.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 1 %

<b>Non-serious adverse events</b>	A GnHR	B Tourniquet	C GnHR and Tourniquet
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	0 / 17 (0.00%)

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 May 2012	Change of IMP formulation from Prostag SR to Prostag SR DCS due to change in formulation by manufacturer. Clarification of route of administration (Intramuscular or Subcutaneous) Clarification of Eligibility criteria and safety reporting requirements (no new criteria just clarification of existing). Clarification of endpoint and statistical requirements (No new information). Administrative changes to protocol wording.
13 September 2018	Protocol was updated to remove secondary endpoints and associated procedures. This trial will now focus on collecting primary endpoint data only.

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Limitations include lower than required number of participants due to a prolonged trial time, changeover of research teams & significant follow up required over the years. Secondary outcomes could not be measured nor impact on QoL.

Notes: