# 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 |

### 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 |
| Scientific contact | Mr Nitish Narvekar, Kings College Hospital Foundation NHS Trust, +44 020 3299 5390, nitish.narvekar@nhs.net |

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 600cm3.

### 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 |

### 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 |
| **Arm title** | A GnHR |

Arm description:

Patients allocated to use of pre-operative GnRH analogues will be prescribed Prostap (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 | prosrap 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:

Prostap (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.

| | |
|---|---|
| **Arm title** | B Tourniquet |

Arm description:

intra-operative mechanical tourniquet only

| | |
|---|---|
| Arm type | surgical intervention |
| No investigational medicinal product assigned in this arm | |
| **Arm title** | C GnHR and Tourniquet |

Arm description:

Prostap (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

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | prosrap SR DCS |
| Investigational medicinal product code | |
| Other name | LEUPRORELIN ACETATE |
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Dosage and administration details:

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| **Number of subjects in period 1[1]** | 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 staring 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 Prostap (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: | |
| Prostap (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<br>Units: Subjects | | | |
| In utero<br>Preterm newborn infants (gestational age < 37 wks)<br>Newborns (0-27 days)<br>Infants and toddlers (28 days-23 months)<br>Children (2-11 years)<br>Adolescents (12-17 years)<br>Adults (18-64 years)<br>From 65-84 years<br>85 years and over | | | |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 40.8 | 39.8 | 41.1 |
| standard deviation | ± 4.7 | ± 5.1 | ± 4.6 |
| Gender categorical<br>Units: Subjects | | | |
| Female | 14 | 12 | 17 |
| Male | 0 | 0 | 0 |
| ethnicity<br>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<br>Units: Subjects | | | |
| No previous births | 11 | 9 | 14 |
| >= 1 birth | 3 | 3 | 3 |
| smoking status<br>Units: Subjects | | | |
| smoker | 1 | 0 | 2 |
| non-smoker | 13 | 12 | 15 |
| BMI<br>Units: kg/m2 | | | |
| arithmetic mean | 29 | 30.9 | 29.8 |
| standard deviation | ± 4.4 | ± 4 | ± 4.3 |

| **Reporting group values** | Total | | |
|---|---|---|---|
| Number of subjects | 43 | | |
| Age categorical<br>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<br>Units: years | | | |
| arithmetic mean | | | |
| standard deviation | - | | |
| Gender categorical<br>Units: Subjects | | | |
| Female | 43 | | |
| Male | 0 | | |
| ethnicity<br>Units: Subjects | | | |
| white | 2 | | |
| black | 40 | | |
| asian | 1 | | |
| Anaemia | | | |
| Hb<12g/L | | | |
| Units: Subjects | | | |
| Hb<12g/L | 8 | | |
| Hb>12g/L | 35 | | |
| Parity<br>Units: Subjects | | | |
| No previous births | 34 | | |
| >= 1 birth | 9 | | |
| smoking status<br>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 Prostap (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: | |
| Prostap (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[1] |
|---|---|
| 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[1]

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 |

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 23.1 |

### Reporting groups

| | |
|---|---|
| Reporting group title | A GnHR |

Reporting group description:

Patients allocated to use of pre-operative GnRH analogues will be prescribed Prostap (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:

Prostap (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 %

| **Non-serious adverse events** | 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 Prostap SR to Prostap SR DCS due to change in formulation by manufacturer.<br>Clarification of route of administration (Intramuscular or Subcutaneous)<br>Clarification of Eligibility criteria and safety reporting requirements (no new criteria just clarification of existing).<br>Clarification of endpoint and statistical requirements (No new information).<br>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:

## 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: