



Clinical trial results:

Pre-surgical metformin for women with endometrial cancer: a randomised placebo controlled trial

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2014-000991-25 |
| Trial protocol | GB |
| Global end of trial date | 02 March 2017 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v1 (current) |
| This version publication date | 09 February 2020 |
| First version publication date | 09 February 2020 |

Trial information

Trial identification

| | |
|-----------------------|--------|
| Sponsor protocol code | R03572 |
|-----------------------|--------|

Additional study identifiers

| | |
|------------------------------------|----------------|
| ISRCTN number | ISRCTN88589234 |
| ClinicalTrials.gov id (NCT number) | - |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Manchester University NHS Foundation Trust |
| Sponsor organisation address | Oxford Road, Manchester, United Kingdom, M13 9WL |
| Public contact | MFT Research Office, Manchester University NHS Foundation Trust, +44 01612763565, lynne.webster@mft.nhs.uk |
| Scientific contact | MFT Research Office, Manchester University NHS Foundation Trust, +44 01612763565, lynne.webster@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 | 02 March 2017 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 02 March 2017 |
| Global end of trial reached? | Yes |
| Global end of trial date | 02 March 2017 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To determine whether metformin has a biological effect on endometrial cancer.

Protection of trial subjects:

Metformin is generally regarded to be safe and is usually well tolerated, patients will be closely monitoring whilst they are taking the IMP. This involves careful review of the patient's medical history and blood results prior to recruitment, provision of contact information to allow the patient to discuss any problems, side effects or safety concerns whilst taking the drug, a telephone call after a few days and again after one to two weeks of commencing treatment with metformin or placebo to check for adverse events and careful questioning of the patient at the end of the study to enquire about difficulties encountered whilst taking metformin.

To improve tolerability, compliance with the study and reduce side effects, we will ask patients to take one 850mg metformin tablet or placebo for the first three days, and increase to two tablets thereafter. Patients who are unable to tolerate treatment with metformin, or who experience serious adverse events whilst taking it will be advised to discontinue treatment.

Patients who have specific contraindications to metformin treatment will not be included in the trial.

Background therapy: -

Evidence for comparator: -

| | |
|---|-------------------|
| Actual start date of recruitment | 01 September 2014 |
| 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: 93 |
| Worldwide total number of subjects | 93 |
| EEA total number of subjects | 93 |

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) | 46 |
| From 65 to 84 years | 46 |
| 85 years and over | 1 |

Subject disposition

Recruitment

Recruitment details:

Subjects were recruited from 4 centres around Greater Manchester - Christie, Penine Acute, Tameside and Wrightington, Wigan and Leigh.

Pre-assignment

Screening details:

Following written informed consent and before commencing treatment with metformin or placebo, the following assessments will be conducted and samples taken:

- ◆ Medical history (to exclude diabetes on treatment, current metformin treatment, severe renal or liver impairment, drug allergy)
- ◆ Height and weight (to calculate BMI)
- ◆ Waist and hip

Period 1

| | |
|------------------------------|--------------------------------|
| Period 1 title | Overall trial (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator |

Blinding implementation details:

Randomisation was provided by Manchester CTU and all information was kept securely within the CTU. Treatment allocation was not made public to investigators or subjects during the trial. Pharmacy had access to an unblinding list in case of emergency unblinding.

Arms

| | |
|------------------------------|-----------|
| Are arms mutually exclusive? | Yes |
| Arm title | Metformin |

Arm description:

Treatment A –Therapeutic arm

Metformin 850mg once a day for 3 days, then twice a day until surgery (between 1 and 5 weeks)

| | |
|--|--------------|
| Arm type | Experimental |
| Investigational medicinal product name | Metformin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Metformin 850mg once a day for 3 days, then twice a day until surgery (between 1 and 5 weeks)

| | |
|------------------|---------|
| Arm title | Placebo |
|------------------|---------|

Arm description:

Treatment B – Control arm

Placebo tablet once a day for 3 days, then twice a day until surgery (between 1 and 5 weeks)

| | |
|--|----------|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Placebo tablet once a day for 3 days, then twice a day until surgery (between 1 and 5 weeks)

| Number of subjects in period 1 | Metformin | Placebo |
|--|-----------|---------|
| Started | 47 | 46 |
| Completed | 45 | 43 |
| Not completed | 2 | 3 |
| Withdrew prior to receiving trial drug | 2 | - |
| Withdrew prior to receiving study drug | - | 2 |
| Surgery postponed | - | 1 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|-----------|
| Reporting group title | Metformin |
|-----------------------|-----------|

Reporting group description:

Treatment A –Therapeutic arm

Metformin 850mg once a day for 3 days, then twice a day until surgery (between 1 and 5 weeks)

| | |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Treatment B – Control arm

Placebo tablet once a day for 3 days, then twice a day until surgery (between 1 and 5 weeks)

| Reporting group values | Metformin | Placebo | Total |
|---|--------------|--------------|-------|
| Number of subjects | 47 | 46 | 93 |
| 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 | | | |
| median | 64.0 | 67.1 | |
| full range (min-max) | 29.6 to 83.7 | 39.8 to 85.2 | - |
| Gender categorical Units: Subjects | | | |
| Female | 47 | 46 | 93 |
| Male | 0 | 0 | 0 |

End points

End points reporting groups

| | |
|---|-----------|
| Reporting group title | Metformin |
| Reporting group description: Treatment A –Therapeutic arm | |
| Metformin 850mg once a day for 3 days, then twice a day until surgery (between 1 and 5 weeks) | |
| Reporting group title | Placebo |
| Reporting group description: Treatment B – Control arm | |
| Placebo tablet once a day for 3 days, then twice a day until surgery (between 1 and 5 weeks) | |

Primary: Post treatment Ki-67 expression

| | |
|---|---------------------------------|
| End point title | Post treatment Ki-67 expression |
| End point description: | |
| End point type | Primary |
| End point timeframe: | |
| Post treatment timepoint adjusted for Baseline expression | |

| End point values | Metformin | Placebo | | |
|---|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 45 | 43 | | |
| Units: % | | | | |
| arithmetic mean (confidence interval 95%) | 32.8 (28.0 to 37.6) | 33.9 (28.2 to 39.7) | | |

Statistical analyses

| | |
|---|--------------------------------|
| Statistical analysis title | Primary Analysis |
| Comparison groups | Metformin v Placebo |
| Number of subjects included in analysis | 88 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[1] |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.57 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -7.57 |
| upper limit | 6.42 |

Notes:

[1] - Linear ANCOVA adjusted for baseline expression

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Timeframe for AE

Adverse event reporting additional description:

AE additional description

| | |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 19.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|-----------|
| Reporting group title | Metformin |
|-----------------------|-----------|

Reporting group description: -

| | |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description: -

| Serious adverse events | Metformin | Placebo | |
|---|----------------|----------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 0 / 46 (0.00%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |

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

| Non-serious adverse events | Metformin | Placebo | |
|---|--------------------------------------|------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 37 / 47 (78.72%) | 25 / 46 (54.35%) | |
| Cardiac disorders | | | |
| PALPITATIONS | Additional description: PALPITATIONS | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 1 / 46 (2.17%) | |
| occurrences (all) | 0 | 2 | |
| Nervous system disorders | | | |
| HEADACHE | Additional description: HEADACHE | | |
| subjects affected / exposed | 5 / 47 (10.64%) | 0 / 46 (0.00%) | |
| occurrences (all) | 5 | 0 | |
| General disorders and administration site conditions | | | |

| | | | |
|-----------------------------|---|-----------------|--|
| DIZZINESS | Additional description: DIZZINESS | | |
| subjects affected / exposed | 3 / 47 (6.38%) | 2 / 46 (4.35%) | |
| occurrences (all) | 3 | 2 | |
| FATIGUE | Additional description: FATIGUE | | |
| subjects affected / exposed | 4 / 47 (8.51%) | 1 / 46 (2.17%) | |
| occurrences (all) | 5 | 1 | |
| NON-SPECIFICALLY UNWELL | Additional description: NON-SPECIFICALLY UNWELL | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 3 / 46 (6.52%) | |
| occurrences (all) | 1 | 3 | |
| Eye disorders | | | |
| BLURRY EYES | Additional description: BLURRY EYES | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 46 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| DRY EYES | Additional description: DRY EYES | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 46 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Gastrointestinal disorders | | | |
| ABDOMINAL PAIN | Additional description: ABDOMINAL PAIN | | |
| subjects affected / exposed | 11 / 47 (23.40%) | 6 / 46 (13.04%) | |
| occurrences (all) | 11 | 6 | |
| ANOREXIA | Additional description: ANOREXIA | | |
| subjects affected / exposed | 9 / 47 (19.15%) | 0 / 46 (0.00%) | |
| occurrences (all) | 9 | 0 | |
| BLOATING/FLATULENCE | Additional description: BLOATING/FLATULENCE | | |
| subjects affected / exposed | 6 / 47 (12.77%) | 2 / 46 (4.35%) | |
| occurrences (all) | 6 | 2 | |
| CONSTIPATION | Additional description: CONSTIPATION | | |
| subjects affected / exposed | 4 / 47 (8.51%) | 1 / 46 (2.17%) | |
| occurrences (all) | 4 | 1 | |
| DIARRHOEA | Additional description: DIARRHOEA | | |
| subjects affected / exposed | 23 / 47 (48.94%) | 6 / 46 (13.04%) | |
| occurrences (all) | 32 | 7 | |
| DRY MOUTH | Additional description: DRY MOUTH | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 3 / 46 (6.52%) | |
| occurrences (all) | 1 | 3 | |
| GASTROESOPHAGEAL REFLUX | Additional description: GASTROESOPHAGEAL REFLUX | | |

| | | | |
|---|---|-----------------|--|
| subjects affected / exposed | 1 / 47 (2.13%) | 3 / 46 (6.52%) | |
| occurrences (all) | 1 | 3 | |
| NAUSEA AND VOMITTING | Additional description: NAUSEA AND VOMITTING | | |
| subjects affected / exposed | 17 / 47 (36.17%) | 6 / 46 (13.04%) | |
| occurrences (all) | 29 | 7 | |
| PARAGEUSIA | Additional description: PARAGEUSIA | | |
| subjects affected / exposed | 3 / 47 (6.38%) | 2 / 46 (4.35%) | |
| occurrences (all) | 3 | 2 | |
| Reproductive system and breast disorders | | | |
| BLEEDING | Additional description: BLEEDING | | |
| subjects affected / exposed | 2 / 47 (4.26%) | 3 / 46 (6.52%) | |
| occurrences (all) | 2 | 3 | |
| HOT FLUSHES | Additional description: HOT FLUSHES | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 46 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| COUGH | Additional description: COUGH | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 1 / 46 (2.17%) | |
| occurrences (all) | 0 | 1 | |
| SHORTNESS OF BREATH | Additional description: SHORTNESS OF BREATH | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 46 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Skin and subcutaneous tissue disorders | | | |
| EXACERBATION OF PSORIASIS | Additional description: EXACERBATION OF PSORIASIS | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 1 / 46 (2.17%) | |
| occurrences (all) | 0 | 1 | |
| RASH/ITCHING | Additional description: RASH/ITCHING | | |
| subjects affected / exposed | 6 / 47 (12.77%) | 2 / 46 (4.35%) | |
| occurrences (all) | 7 | 3 | |
| Renal and urinary disorders | | | |
| IMPAIRED RENAL FUNCTION | Additional description: IMPAIRED RENAL FUNCTION | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 46 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Endocrine disorders | | | |
| HUNGRY FOR SUGAR | Additional description: HUNGRY FOR SUGAR | | |

| | | | |
|---|--------------------------------------|----------------|--|
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 46 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| BACK PAIN | Additional description: BACK PAIN | | |
| subjects affected / exposed | 2 / 47 (4.26%) | 0 / 46 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| LEG CRAMPS | Additional description: LEG CRAMPS | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 46 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| MUSCLE ACHES | Additional description: MUSCLE ACHES | | |
| subjects affected / exposed | 2 / 47 (4.26%) | 0 / 46 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Infections and infestations | | | |
| TOOTH ABCESS | Additional description: TOOTH ABCESS | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 1 / 46 (2.17%) | |
| occurrences (all) | 0 | 1 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 17 November 2014 | Change of trial name to assist with public engagement. Addition of omental biopsy during hysterectomy to enable exploratory work investigating the effect of metformin on adipose tissue proliferation, metabolism and communication with endometrial cancer cells through the generation of a novel adipocyte and endometrial cancer cell co-culture system. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported