



Clinical trial results:

Proof of mechanism pre-surgical window trial of metformin in non-diabetic women with endometrial carcinoma: a feasibility study

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2011-001382-40 |
| Trial protocol | GB |
| Global end of trial date | 30 June 2015 |

Results information

| | |
|--------------------------------|---------------|
| Result version number | v1 (current) |
| This version publication date | 25 April 2020 |
| First version publication date | 25 April 2020 |

Trial information

Trial identification

| | |
|-----------------------|--------|
| Sponsor protocol code | R01602 |
|-----------------------|--------|

Additional study identifiers

| | |
|------------------------------------|---------------------------|
| ISRCTN number | ISRCTN81570194 |
| ClinicalTrials.gov id (NCT number) | - |
| WHO universal trial number (UTN) | - |
| Other trial identifiers | REF reference: 11/NW/0442 |

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, Manchester University NHS Foundation Trust, +44 01612764125, research.sponsor@mft.nhs.uk |
| Scientific contact | Dr Lynne Webster, Manchester University NHS Foundation Trust, +44 01612764125, 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 | 30 July 2015 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 26 February 2014 |
| Global end of trial reached? | Yes |
| Global end of trial date | 30 June 2015 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To determine whether metformin exerts any effect when given prior to hysterectomy surgery in non diabetic women with endometrial cancer.

Protection of trial subjects:

Interviews and biological samples will be collected at a time when the patient would already be in the clinic being reviewed by clinical staff. This can be rescheduled if not convenient.

The endometrial biopsies were only taken by senior experienced clinicians with expertise in this potentially embarrassing and uncomfortable procedure. There were female chaperones present at all intimate examinations. The examination would have been abandoned if the patient told us they were finding it extremely painful.

Although the safety profile of Metformin is well known and well tolerated, its use in women with endometrial cancer was not known. We therefore closely monitored the patients whilst they are taking the drug. Any safety concerns were recorded. Any patients unable to tolerate metformin or who experience serious adverse events whilst taking it will be advised to discontinue treatment.

Background therapy:

There is no background therapy for the trial.

Evidence for comparator:

Metformin is the only drug in the trial, there is no comparator drug.

| | |
|---|------------------|
| Actual start date of recruitment | 09 November 2011 |
| 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: 36 |
| Worldwide total number of subjects | 36 |
| EEA total number of subjects | 36 |

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 | 0 |

| | |
|---------------------------|----|
| months) | |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 20 |
| From 65 to 84 years | 16 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

36 patients were recruited to the metformin arm - 35 received the treatment and 1 was a screen failure. 15 patients were recruited to the untreated control arm of the trial.

Pre-assignment

Screening details:

101 patients were screened for eligibility between October 2012 and February 2014. 65 were not eligible or declined the metformin treatment.

Period 1

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

Blinding implementation details:

This was a single-arm trial with no control.

Arms

| | |
|-----------|-------------------|
| Arm title | Metformin-treated |
|-----------|-------------------|

Arm description:

Women were given Metformin 850mg BD for 2-4 weeks until surgery.

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

Dosage and administration details:

Maximum allowed dose: 1700mg per day. Maximum duration of treatment: 4 weeks. Boxes of coated tablets of metformin hydrochloride 850mg will be supplied to study participants on the second visit after obtaining fasted blood samples and the endometrial biopsy. To enable the return of the IMP, a prepaid addressed envelope will be provided at the second visit. Each patient will take one 850mg tablet twice a day from recruitment into the study until surgery (at least two weeks and up to four weeks total time period). The number of tablets dispensed will be fifty-six in all cases. Boxes will be dispensed by the Clinical Trials Pharmacy at CMFT and labelled as Investigational Medicinal Product (IMP). Boxes will be prescribed for an individual, named patient who has provided written informed consent to participate in the trial. Boxes of metformin will be stored in the pharmacy according to the manufacturer's instructions until suitable patients are recruited.

| Number of subjects in period 1 | Metformin-treated |
|--------------------------------|-------------------|
| Started | 36 |
| Completed | 35 |
| Not completed | 1 |
| Screen failure | 1 |

Period 2

| | |
|------------------------------|------------------|
| Period 2 title | Treatment period |
| Is this the baseline period? | No |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

Blinding implementation details:

This was a single arm trial with no control.

Arms

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

Dosage and administration details:

Maximum allowed dose: 1700mg per day. Maximum duration of treatment: 4 weeks. Boxes of coated tablets of metformin hydrochloride 850mg will be supplied to study participants on the second visit after obtaining fasted blood samples and the endometrial biopsy. To enable the return of the IMP, a prepaid addressed envelope will be provided at the second visit. Each patient will take one 850mg tablet twice a day from recruitment into the study until surgery (at least two weeks and up to four weeks total time period). The number of tablets dispensed will be fifty-six in all cases. Boxes will be dispensed by the Clinical Trials Pharmacy at CMFT and labelled as Investigational Medicinal Product (IMP). Boxes will be prescribed for an individual, named patient who has provided written informed consent to participate in the trial. Boxes of metformin will be stored in the pharmacy according to the manufacturer's instructions until suitable patients are recruited.

| Number of subjects in period 2 | Metformin |
|--------------------------------|-----------|
| Started | 35 |
| Completed | 28 |
| Not completed | 7 |
| Adverse event, non-fatal | 4 |
| Protocol deviation | 3 |

Baseline characteristics

Reporting groups

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

Reporting group description:

Women were given Metformin 850mg BD for 2-4 weeks until surgery.

| Reporting group values | Metformin-treated | Total | |
|-----------------------------------|-------------------|-------|--|
| Number of subjects | 36 | 36 | |
| Age categorical | | | |
| Units: Subjects | | | |
| Less than 50 | 2 | 2 | |
| 51-60 | 14 | 14 | |
| 61-70 | 14 | 14 | |
| 71-80 | 5 | 5 | |
| Greater than 80 | 1 | 1 | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 62.0 | | |
| standard deviation | ± 9.8 | - | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 36 | 36 | |
| Male | 0 | 0 | |
| BMI | | | |
| Units: Subjects | | | |
| Less than 25 | 6 | 6 | |
| 25-29.9 | 8 | 8 | |
| 30-39.9 | 10 | 10 | |
| Greater than 40 | 11 | 11 | |
| Missing | 1 | 1 | |
| Smoking habits | | | |
| Units: Subjects | | | |
| Nonsmoker | 18 | 18 | |
| Ex-smoker | 12 | 12 | |
| Current smoker | 5 | 5 | |
| Missing | 1 | 1 | |
| Daily alcoholic units | | | |
| Units: Subjects | | | |
| None | 14 | 14 | |
| Less than or equal to 2 | 11 | 11 | |
| Greater than 2 | 2 | 2 | |
| Missing | 9 | 9 | |
| Insulin resistance | | | |
| Units: Subjects | | | |
| HOMA-IR greater than 2.8 | 18 | 18 | |
| HOMA-IR less than or equal to 2.8 | 17 | 17 | |
| Missing | 1 | 1 | |
| Tumour grade at hysterectomy | | | |

| | | | |
|---------------------------------------|----|----|--|
| Units: Subjects | | | |
| AEH | 0 | 0 | |
| G1 | 17 | 17 | |
| G2 | 14 | 14 | |
| G3 | 4 | 4 | |
| Missing | 1 | 1 | |
| FIGO stage at hysterectomy | | | |
| Units: Subjects | | | |
| 1A | 20 | 20 | |
| 1B | 3 | 3 | |
| Two | 2 | 2 | |
| Three | 3 | 3 | |
| Missing | 8 | 8 | |
| Lymphovascular space invasion present | | | |
| Units: Subjects | | | |
| Yes | 12 | 12 | |
| No | 20 | 20 | |
| Missing | 4 | 4 | |
| Myometrial invasion | | | |
| Units: Subjects | | | |
| Less than 50% | 23 | 23 | |
| Greater than or equal to 50% | 8 | 8 | |
| Missing | 5 | 5 | |
| Follow-up and adjuvant therapy | | | |
| Units: Subjects | | | |
| Clinical follow-up | 20 | 20 | |
| Chemotherapy alone | 4 | 4 | |
| Chemotherapy, EBRT & VB | 5 | 5 | |
| VB: Vaginal brachytherapy | 2 | 2 | |
| EBRT: External beam radiotherapy | 1 | 1 | |
| Missing | 3 | 3 | |
| VB & EBRT | 1 | 1 | |
| ER expression | | | |
| Units: Subjects | | | |
| Positive | 28 | 28 | |
| Negative | 0 | 0 | |
| Missing | 8 | 8 | |
| PR expression | | | |
| Units: Subjects | | | |
| Positive | 28 | 28 | |
| Negative | 0 | 0 | |
| Missing | 8 | 8 | |
| PTEN expression | | | |
| Units: Subjects | | | |
| Wild type | 19 | 19 | |
| Mutant | 9 | 9 | |
| Missing | 8 | 8 | |
| P53 expression | | | |
| Units: Subjects | | | |
| Wild type | 27 | 27 | |
| Mutant | 1 | 1 | |

| | | | |
|---------|---|---|--|
| Missing | 8 | 8 | |
|---------|---|---|--|

| | | | |
|---|-------------------|---|--|
| BMI Units: kg m-2 arithmetic mean standard deviation | 35.3 ± 11.2 | - | |
| Waist/hip girth ratio Units: ratio arithmetic mean standard deviation | 0.88 ± 0.06 | - | |
| HOMA-IR index Units: Index arithmetic mean standard deviation | 3.97 ± 2.62 | - | |
| Ki-67 proliferation index Units: Percentage arithmetic mean standard deviation | 50.9 ± 17.1 | - | |
| Glucose Units: mmol/l arithmetic mean standard deviation | 6.0 ± 1.5 | - | |
| Insulin Units: mU/l arithmetic mean standard deviation | 16.0 ± 9.4 | - | |
| C-peptide Units: pmol/l arithmetic mean standard deviation | 1076.1 ± 482.3 | - | |
| Adiponectin Units: mg/l arithmetic mean standard deviation | 3.3 ± 1.5 | - | |
| Leptin Units: mg/ml arithmetic mean standard deviation | 54.1 ± 42.6 | - | |
| Ln (hsCRP) Units: mg/l arithmetic mean standard deviation | 1.3 ± 1.3 | - | |

End points

End points reporting groups

| | |
|--|-------------------|
| Reporting group title | Metformin-treated |
| Reporting group description: Women were given Metformin 850mg BD for 2-4 weeks until surgery. | |
| Reporting group title | Metformin |
| Reporting group description: - | |

Primary: Ki-67 proliferation

| | |
|------------------------|------------------------------------|
| End point title | Ki-67 proliferation ^[1] |
| End point description: | |
| End point type | Primary |
| End point timeframe: | |
| Post-treatment | |

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: Patients in this study were compared to a non-randomised control group of individuals recruited onto an independent study. There were no separate statistical analyses for the Metformin data alone. In our paper, the primary endpoint, change in tumour Ki-67 proliferation index after adjustment for baseline Ki-67, age, BMI, insulin resistance and change in the control group was found to be -17.2 (95% CI -27.4, -4.0%), compared to 13.5% (SD 15.5) for the Metformin group alone.

| End point values | Metformin | | | |
|--------------------------------------|-----------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 28 | | | |
| Units: Percentage | | | | |
| arithmetic mean (standard deviation) | 37.4 (± 29.0) | | | |

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: | |
| Post-treatment | |

| | | | | |
|--------------------------------------|------------------|--|--|--|
| End point values | Metformin | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 28 | | | |
| Units: mmol/l | | | | |
| arithmetic mean (standard deviation) | 5.5 (\pm 1.3) | | | |

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: | |
| Post-treatment | |

| | | | | |
|--------------------------------------|------------------|--|--|--|
| End point values | Metformin | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 28 | | | |
| Units: mU/l | | | | |
| arithmetic mean (standard deviation) | 9.9 (\pm 7.1) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: HOMA-IR

| | |
|------------------------|-----------|
| End point title | HOMA-IR |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| Post-treatment | |

| | | | | |
|--------------------------------------|-----------------|--|--|--|
| End point values | Metformin | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 28 | | | |
| Units: Scale | | | | |
| arithmetic mean (standard deviation) | 2.5 (± 2.0) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: C-peptide

| | |
|------------------------|-----------|
| End point title | C-peptide |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| Post-treatment | |

| | | | | |
|--------------------------------------|-----------------|--|--|--|
| End point values | Metformin | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 28 | | | |
| Units: pmol/l | | | | |
| arithmetic mean (standard deviation) | 985.4 (± 525.3) | | | |

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: | |
| Post-treatment | |

| | | | | |
|--------------------------------------|------------------|--|--|--|
| End point values | Metformin | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 28 | | | |
| Units: mg/l | | | | |
| arithmetic mean (standard deviation) | 2.8 (\pm 1.1) | | | |

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: | |
| Post-treatment | |

| | | | | |
|--------------------------------------|--------------------|--|--|--|
| End point values | Metformin | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 28 | | | |
| Units: ng/ml | | | | |
| arithmetic mean (standard deviation) | 57.9 (\pm 46.7) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Ln(hsCRP)

| | |
|------------------------|-----------|
| End point title | Ln(hsCRP) |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| Post-treatment | |

| | | | | |
|--------------------------------------|------------------|--|--|--|
| End point values | Metformin | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 28 | | | |
| Units: mg/l | | | | |
| arithmetic mean (standard deviation) | 0.8 (\pm 1.4) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Body mass index

| | |
|------------------------|-----------------|
| End point title | Body mass index |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| Post-treatment | |

| | | | | |
|--------------------------------------|--------------------|--|--|--|
| End point values | Metformin | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 28 | | | |
| Units: kg/m ² | | | | |
| arithmetic mean (standard deviation) | 35.1 (\pm 10.9) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Waist/hip girth ratio

| | |
|------------------------|-----------------------|
| End point title | Waist/hip girth ratio |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| Post-treatment | |

| | | | | |
|--------------------------------------|------------------|--|--|--|
| End point values | Metformin | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 28 | | | |
| Units: Ratio | | | | |
| arithmetic mean (standard deviation) | 0.9 (\pm 0.1) | | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Patients will be contacted by telephone after one to two weeks of metformin treatment to ensure tolerability and to check for adverse events.

Adverse event reporting additional description:

Any SAE will be reported by the Principal Investigator (including a completed SAE form) within 24 hours of first knowledge to the Sponsor. The Principal Investigator will ensure that the patient is appropriately treated. They will also determine whether the SAE is a SUSAR (Suspected Unexpected Serious Adverse Reaction).

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

Dictionary used

| | |
|--------------------|--------|
| Dictionary name | MedDRA |
| Dictionary version | 1 |

Reporting groups

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

Reporting group description: -

| Serious adverse events | Metformin | | |
|---|---|--|--|
| 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 | | |
| Cardiac disorders | | | |
| Atrial fibrillation | Additional description: Patient 020 (14th August 2013): Atrial fibrillation (hospitalisation); unlikely to be related to study IMP. | | |
| 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 %

| Non-serious adverse events | Metformin | | |
|---|--|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 27 / 35 (77.14%) | | |
| Investigations | | | |
| Abnormal baseline bloods | Additional description: 10 participants experienced this AE. | | |
| subjects affected / exposed | 10 / 35 (28.57%) | | |
| occurrences (all) | 10 | | |
| Nervous system disorders | | | |

| | | | |
|--|--|--|--|
| Headache subjects affected / exposed occurrences (all) | Additional description: 3 participants experienced this AE. | | |
| | 3 / 35 (8.57%) | | |
| | 3 | | |
| General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all) | Additional description: 2 participants experienced this AE. | | |
| | 2 / 35 (5.71%) | | |
| | 2 | | |
| Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) Loss of appetite subjects affected / exposed occurrences (all) Nausea/vomiting subjects affected / exposed occurrences (all) Abdominal pain subjects affected / exposed occurrences (all) Bloating subjects affected / exposed occurrences (all) | Additional description: 24 participants experienced this AE. | | |
| | 24 / 35 (68.57%) | | |
| | 24 | | |
| | Additional description: 4 participants experienced this AE. | | |
| | 4 / 35 (11.43%) | | |
| | 4 | | |
| | Additional description: 27 participants experienced this AE. | | |
| | 27 / 35 (77.14%) | | |
| | 27 | | |
| | Additional description: 12 participants experienced this AE. | | |
| | 12 / 35 (34.29%) | | |
| | 12 | | |
| | Additional description: 2 participants experienced this AE. | | |
| | 2 / 35 (5.71%) | | |
| | 2 | | |
| Reproductive system and breast disorders Others subjects affected / exposed occurrences (all) | Additional description: 11 participants experienced other AEs. | | |
| | 11 / 35 (31.43%) | | |
| | 11 | | |
| Skin and subcutaneous tissue disorders Skin changes subjects affected / exposed occurrences (all) | Additional description: 3 participants experienced this AE. | | |
| | 3 / 35 (8.57%) | | |
| | 3 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 21 December 2011 | Substantial amendment 1: (1) To restrict entry to the study to patients with type 1 endometrial cancer. (2) To perform some laboratory analysis at the Wolfson Molecular Imaging Centre. (3) To ask participants to return to St Mary's to have their final blood test and endometrial biopsy taken ahead of surgery in the event that surgery is delayed beyond four weeks. (4) To amend the PIS to reflect the above changes. This amendment also required a change to the protocol (V3.0). R&D approval for the amendment was issued 26/01/2012. |
| 29 August 2012 | Substantial amendment 2: (1) To state that a Part 1 of the Participant Information Sheet will be sent to potential participants with their letter inviting them to attend their pre-operative gynaecological clinic. (2) To clarify that two visits will be required in order to obtain blood samples prior to starting treatment with metformin. (3) To update the Participant Information Sheet to reflect the above change (point 2). (4) To amend the Protocol to state that metformin will be dispensed at the pre-admission clinic and participants instructed to begin treatment if the renal function is within permissible range. (5) To make a number of minor changes to the Protocol. This amendment updated the protocol to V4.0. R&D approval was issued 21/09/2012. |
| 01 February 2013 | Substantial amendment 4: Amendment to include patients with atypical hyperplasia and patients with shorter window periods to increase participant numbers. This amendment updated the protocol to V5.0. R&D approval was issued 14/03/2013. |

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.

N/A

Notes:

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/26794276>