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	35.3		
standard deviation	± 11.2	-	
Waist/hip girth ratio			
Units: ratio			
arithmetic mean	0.88		
standard deviation	± 0.06	-	
HOMA-IR index			
Units: Index			
arithmetic mean	3.97		
standard deviation	± 2.62	-	
Ki-67 proliferation index			
Units: Percentage			
arithmetic mean	50.9		
standard deviation	± 17.1	-	
Glucose			
Units: mmol/l			
arithmetic mean	6.0		
standard deviation	± 1.5	-	
Insulin			
Units: mU/l			
arithmetic mean	16.0		
standard deviation	± 9.4	-	
C-peptide			
Units: pmol/l			
arithmetic mean	1076.1		
standard deviation	± 482.3	-	
Adiponectin			
Units: mg/l			
arithmetic mean	3.3		
standard deviation	± 1.5	-	
Leptin			
Units: mg/ml			
arithmetic mean	54.1		
standard deviation	± 42.6	-	
Ln (hsCRP)			
Units: mg/l			
arithmetic mean	1.3		
standard deviation	± 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 (± 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 (± 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 (± 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 (± 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 (± 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/m2				
arithmetic mean (standard deviation)	35.1 (± 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 (± 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	Additional description: 3 participants experienced this AE.		
subjects affected / exposed	3 / 35 (8.57%)		
occurrences (all)	3		
General disorders and administration site conditions			
Fatigue	Additional description: 2 participants experienced this AE.		
subjects affected / exposed	2 / 35 (5.71%)		
occurrences (all)	2		
Gastrointestinal disorders			
Diarrhoea	Additional description: 24 participants experienced this AE.		
subjects affected / exposed	24 / 35 (68.57%)		
occurrences (all)	24		
Loss of appetite	Additional description: 4 participants experienced this AE.		
subjects affected / exposed	4 / 35 (11.43%)		
occurrences (all)	4		
Nausea/vomiting	Additional description: 27 participants experienced this AE.		
subjects affected / exposed	27 / 35 (77.14%)		
occurrences (all)	27		
Abdominal pain	Additional description: 12 participants experienced this AE.		
subjects affected / exposed	12 / 35 (34.29%)		
occurrences (all)	12		
Bloating	Additional description: 2 participants experienced this AE.		
subjects affected / exposed	2 / 35 (5.71%)		
occurrences (all)	2		
Reproductive system and breast disorders			
Others	Additional description: 11 participants experienced other AEs.		
subjects affected / exposed	11 / 35 (31.43%)		
occurrences (all)	11		
Skin and subcutaneous tissue disorders			
Skin changes	Additional description: 3 participants experienced this AE.		
subjects affected / exposed	3 / 35 (8.57%)		
occurrences (all)	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 they 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