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 involvde 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 recieving 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