Clinical trial results:
A randomized, double-blind, parallel group, placebo-controlled trial of metformin in tuberous sclerosis complex.

Summary

EudraCT number	2011-001319-30
Trial protocol	GB
Global end of trial date	28 February 2017

Results information

Result version number	v1 (current)
This version publication date	27 September 2018
First version publication date	27 September 2018

Trial information

Trial identification

Sponsor protocol code	CH/2011/3670

Additional study identifiers

ISRCTN number	ISRCTN92545532
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University Hospitals Bristol NHS Foundation Trust
Sponsor organisation address	Upper Maudlin street, Bristol , Bristol, United Kingdom, BS28AE
Public contact	Jessica Bisset Research operational Manager University Hospitals Bristol NHS Foundation Trust , University Hospitals Bristol NHS Foundation Trust , 0117 3420233, r&dsponsorship@uhbristol.nhs.uk
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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	27 May 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	28 February 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Does the drug metformin reduce the size of kidney tumours in people with Tuberous Sclerosis Complex?

Protection of trial subjects:

regular follow up and contact with patients to ensure safety
local GPs are informed about this trial so that they are aware and protect patients

Background therapy:

The drug metformin works on the part of the body's cells that controls growth, and might provide an alternative way to control cell growth. If it does, then treatment with metformin could slow down, stop or even reverse the growth of tumours in TSC. Metformin has been shown to reduce the growth of some tumours growing in test-tubes and in mice, and is associated with a lower risk of development of cancerous tumours in some patients.
This study is testing the idea that metformin is effective in reducing the size of kidney tumours in people with TSC. It is a randomised double-blind placebo controlled trial. Half will take metformin and half will take a sugar-pill
(placebo) for 12 months. All will have regular checks for side effects. All will have scans at the start, 6, 12 and 18 months to monitor tumour size. At the same times they will have evaluations of their facial and nail tumours and epilepsy severity. At the start of the study and at 12 months they will have evaluations of their cognitive abilities and their quality of life.

Evidence for comparator:

Rapamycin and Everolimus are drugs that are known to inhibit mTOR and studies have shown that they can reduce TSC-related kidney and brain tumour size. They can cause significant side effects and their long term effect is unknown. In addition, they are very expensive drugs.

Metformin is a drug that potentially offers the benefit of mTOR inhibition without the side effect profile of rapamycin. It is used by millions of people with type 2 diabetes and has a very benign side effect profile. It does not lower blood sugar in non-diabetic people unless given in overdose. It has recently been shown to inhibit mTOR and has been used to inhibit the growth of cancerous cells (breast cancer and squamous cell carcinoma cells) in vitro via this mTOR inhibition. It has been shown to kill human breast cancer cells in a mouse model and was used in this mouse model at concentrations lower than typically used for the treatment of diabetes. It is hypothesised that metformin will reduce TSCrelated tumour size via inhibition of mTOR

Actual start date of recruitment	13 November 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 55

Worldwide total number of subjects	55
EEA total number of subjects	55

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)	2
Adolescents (12-17 years)	9
Adults (18-64 years)	44
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were recruited from three specialist TSC clinics in Bath, Bristol and London in the United Kingdom. Prior to their standard clinic appointment, all clinic patients were sent a letter introducing the study (including participant information sheets and study team contact details).

Pre-assignment

Screening details:

72 patients assessed for eligibility
1 declined due to placebo
5 declined – no reason
9 not eligible
2 unwell

55 enrolled and randomly assigned

4 did not start treatment:
Mother changed mind
Decided to take part in another study
Busy life style change
One did not start due to social reason

Period 1

Period 1 title	treatment period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

Patients were randomly allocated (1:1) to placebo or metformin for 12 months. The randomisation was stratified by centre and minimised by age-group (10 to <20; 20 to <30; 30 to <40; and 40 to <65) and by the presence or absence of learning disabilities. The randomisation was concealed. The investigators randomised patients online, and wrote randomisation number and treatment pack number on the study prescription form

Arms

Are arms mutually exclusive?	Yes
Arm title	Metformin arm

Arm description:

Patients received metformin for 12 months

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:

For adult patients, the starting dose was 500mg twice a day orally. At 6 months, the dose was escalated to 500mg three times a day as long as the patient was tolerating the treatment. For children aged 10-16 years, the drug dosing started at 500mg once a day. After two weeks at this dose, it was escalated to 500mg twice a day. At 6 months the dose was escalated to 500mg three times a day as long as the patient was tolerating treatment well.

Arm title	placebo

Arm description:

patients received placebo

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:

For adult patients, the starting dose was 500mg twice a day orally. At 6 months, the dose was escalated to 500mg three times a day as long as the patient was tolerating the treatment. For children aged 10-16 years, the drug dosing started at 500mg once a day. After two weeks at this dose, it was escalated to 500mg twice a day. At 6 months the dose was escalated to 500mg three times a day as long as the patient was tolerating treatment well.

Number of subjects in period 1	Metformin arm	placebo
Started	28	27
Completed	27	24
Not completed	1	3
Consent withdrawn by subject	1	3

Baseline characteristics

Reporting groups	
Reporting group title	treatment period

Reporting group description: -

Reporting group values	treatment period	Total	
Number of subjects	55	55	
Age categorical			
The randomisation was stratified by centre and minimised by age-group (10 to <20; 20 to <30; 30 to <40; and 40 to <65)			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	2	2	
Adolescents (12-17 years)	8	8	
Adults (18-64 years)	45	45	
From 65-84 years	0	0	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	29	29	
Male	26	26	

Subject analysis sets	
Subject analysis set title	primary and secondary outcomes
Subject analysis set type	Full analysis

Subject analysis set description:
full analysis performed

Reporting group values	primary and secondary outcomes		
Number of subjects	51		
Age categorical			
The randomisation was stratified by centre and minimised by age-group (10 to <20; 20 to <30; 30 to <40; and 40 to <65)			
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)	2		
Adolescents (12-17 years)	7		
Adults (18-64 years)	42		

From 65-84 years	0		
85 years and over	0		

Gender categorical Units: Subjects			
Female	25		
Male	26		

End points

End points reporting groups

Reporting group title	Metformin arm
Reporting group description: Patients received metformin for 12 months	
Reporting group title	placebo
Reporting group description: patients received placebo	
Subject analysis set title	primary and secondary outcomes
Subject analysis set type	Full analysis
Subject analysis set description: full analysis performed	

Primary: primary end point

End point title	primary end point
End point description:	
End point type	Primary
End point timeframe: 12 months	

End point values	Metformin arm	placebo	primary and secondary outcomes	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	27	24	51[1]	
Units: 9 to 41				
number (confidence interval 95%)	27 (9 to 41)	24 (9 to 41)	0 (0 to 0)	

Notes:

[1] - this is for AML volume

Statistical analyses

Statistical analysis title	Two-tailed t-tests

Statistical analysis description:

Analysis was by intention to treat. The primary analysis of effectiveness was a comparison of the percentage volume change of renal AMLs in the metformin and placebo arms. Two-tailed t-tests were used to compare the mean percentage change in each group. The secondary outcome variables were analysed as the primary outcomes.

Comparison groups	placebo v Metformin arm v primary and secondary outcomes
Number of subjects included in analysis	102
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.221
Method	t-test, 2-sided
Parameter estimate	Median difference (net)
Point estimate	15.9

Confidence interval	
level	95 %
sides	2-sided
lower limit	-9
upper limit	41
Variability estimate	Standard deviation

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 18 months during the trial and 6 month post trial	
Assessment type	Systematic

Dictionary used	
Dictionary name	Not used
Dictionary version	1

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	3 / 27 (11.11%)	0 / 24 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Nervous system disorders			
Seizure			
subjects affected / exposed	1 / 27 (3.70%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pneumothorax spontaneous			
subjects affected / exposed	1 / 27 (3.70%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
kidney bleeding			
subjects affected / exposed	2 / 27 (7.41%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Metformin	placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 27 (29.63%)	3 / 24 (12.50%)	
Injury, poisoning and procedural complications			
fall			
subjects affected / exposed	1 / 27 (3.70%)	0 / 24 (0.00%)	
occurrences (all)	0	0	
Nervous system disorders			
seizure			
subjects affected / exposed	1 / 27 (3.70%)	0 / 24 (0.00%)	
occurrences (all)	0	0	
Headache			
subjects affected / exposed	1 / 27 (3.70%)	1 / 24 (4.17%)	
occurrences (all)	0	0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 27 (3.70%)	0 / 24 (0.00%)	
occurrences (all)	0	0	
gastric upset			
subjects affected / exposed	1 / 27 (3.70%)	0 / 24 (0.00%)	
occurrences (all)	0	0	
food poisoning			
subjects affected / exposed	1 / 27 (3.70%)	0 / 24 (0.00%)	
occurrences (all)	0	0	
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 27 (3.70%)	0 / 24 (0.00%)	
occurrences (all)	0	0	
Renal and urinary disorders			
Urinary tract infection			
subjects affected / exposed	1 / 27 (3.70%)	0 / 24 (0.00%)	
occurrences (all)	0	0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 27 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	0	

dental infection subjects affected / exposed occurrences (all)	0 / 27 (0.00%) 0	1 / 24 (4.17%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 January 2014	Chief Investigator - change of employer; change of Principal Investigator at site; addition of a new site

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported