



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 |
| Scientific contact | University Hospitals Bristol NHS Foundation Trust , University Hospitals Bristol NHS Foundation Trust , 0117 3420204, sam.amin.14@ucl.ac.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 | 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 TSC-related 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:

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| 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 | |

| 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 | 0 / 27 (0.00%) | 1 / 24 (4.17%) | |
| occurrences (all) | 0 | 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