A randomised, double blind, placebo-controlled study of RAD001 (Everolimus) in the treatment of neurocognitive problems in tuberous sclerosis

Submission date 07/11/2011	Recruitment status No longer recruiting		
Registration date 28/12/2011	Overall study status Completed		
Last Edited 28/03/2023	Condition category Nervous System Diseases		

[X] Prospectively registered

[X] Protocol

[X] Statistical analysis plan

- [X] Results
- [] Individual participant data

Plain English summary of protocol

Background and study aims

Tuberous sclerosis (TSC) is a genetic disorder affecting approximately 1 in 10,000 people. It is characterised by the development of tumours in many organs and can lead to seizures, neurocognitive difficulties and behavioural and developmental disorders. These brain-related problems occur in the majority of those with TSC and were rated as being the most significant part of the disease by patients and families because of their everyday impact on education, employment, family and social life. The potential benefits of better treatment therefore include both a reduction in health care demands and wider benefits for patients and their carers. In the past it was thought that many of the problems caused by TSC might be entirely due to tumours in the brains of sufferers. However, recent research suggests that not only might gene mutation also play a major role but it is also possibly reversible. Studies have shown that certain drugs can be used to reduce the size of tumours. The main aim of this study is to see how the use of a drug named Everolimus affects recall memory and executive function of those with TSC over a period of 6 months.

Who can participate?

Participants need to be aged 16 to 60 years and have an IQ of more than 60. Both males and females can take part in the study. Only people with TSC will be able to take part.

What does the study involve?

Before starting, you will be asked to have some tests that help the doctor to decide if you can take part in the research. If the doctor thinks you can take part you will also be asked to come back to the hospital about every 2 weeks to begin with and then with longer gaps between visits as time goes on, for 9 months. The tests you may have as part of this research include:

- 1. The doctor will talk to you about how you feel.
- 2. The doctor will examine you.
- 3. You will have a test to find out how well your lungs work.
- 4. You will have a test to measure your heartbeat (Electrocardiogram (ECG)).

5. The doctor or nurse will take a blood sample from you.

6. You will be asked to provide a urine sample.

7. The research psychologist will do some memory and thinking tests with you.

In this research some people taking part will receive the medicine we are testing and other people will receive a 'dummy medicine' that looks exactly the same but does not contain any active ingredients. Neither you nor the research doctor can choose whether you will get the study medicine or the dummy medicine and you will not know which one you are taking throughout the study.

You will be asked to take tablets (2 for most people, but this may vary) once a day by mouth at about the same time of day.

You may either take the tablets with a glass of water or apple juice or after a light meal. If you find this difficult you may instead dissolve the tablets in a glass of water and drink the mixture. If you have problems taking the medicine please tell the research doctor and the person who comes with you to the research clinic.

Whilst taking part in the research you will be asked to avoid grapefruit, Seville oranges (including marmalade), and star fruit and the juices of these fruits as they can cause problems with the medicine.

A drug called Everolimus will be compared against a placebo. One third of the participants will receive the placebo while two-thirds will receive the drug Everolimus but this is decided at random.

What are the possible benefits and risks of participating?

The potential benefits of taking part include both a reduction in health care demands and a reduction is the amount of neuro-cognitive difficulties experienced. Possible side effects of the medicine include mouth ulcers, feeling tired, weak and sick, being sick, skin rash, problems going to the toilet, not feeling very hungry, swelling in your legs, feeling hot, having an odd taste in your mouth, nose bleeds, pain in your arms and/or legs, shortness of breath, dry skin and headache. However, there will be a doctor will be able to help decide how best to deal with any side effect.

Where is the study run from?

The study is open to people from all over the UK but it will take place at University Hospital Wales, Cardiff.

When is the study starting and how long is it expected to run for? The study is due to start recruiting participants at the end of December 2011. The trial will be recruiting participants for 12 months.

Who is funding the study?

The study is being run by Cardiff University but funded by pharmaceutical company Novartis.

Who is the main contact? Dr Cheney Drew (public contact), drewc5@cardiff.ac.uk (added 24/04/2019) Professor Julian Sampson (scientific contact), sampson@cardiff.ac.uk

Contact information

Type(s) Scientific

Contact name

Prof Julian Sampson

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Type(s)

Public

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Additional identifiers

EudraCT/CTIS number 2011-004854-25

IRAS number

ClinicalTrials.gov number NCT01954693

Secondary identifying numbers SPON803-10

Study information

Scientific Title

A randomised, double blind, placebo-controlled study of RAD001 (Everolimus) in the TReatment Of Neurocognitive problems in tuberous sclerosis (TRON)

Acronym

TRON

Study objectives

Are the recall memory and executive function in people with tuberous sclerosis (TSC) improved after treatment with RAD001 (Everolimus) or placebo for 6 months?

Ethics approval required

Old ethics approval format

Ethics approval(s)

Approved 09/11/2011, Wales REC 3 (Health and Care Research Support Centre, Castlebridge 4, 15-19 Cowbridge Road East, Cardiff, CF11 9AB, UK; +44 (0)29 20785741; Wales.REC3@wales.nhs. uk), ref: 11/WA/0308

Study design

Single-centre two-arm individually randomised phase II double-blind placebo-controlled trial

Primary study design Interventional

Secondary study design Randomised controlled trial

Study setting(s) Hospital

Study type(s) Treatment

Participant information sheet

Not available in web format, please use the contact details below to request a patient information sheet

Health condition(s) or problem(s) studied

Tuberous sclerosis

Interventions

RAD001 (Everolimus) versus placebo in the treatment of neurocognitive problems in patients with tuberous sclerosis (TSC)

Intervention Type

Drug

Phase Phase II

Drug/device/biological/vaccine name(s)

Everolimus

Primary outcome measure

- 1. List Learning test (from the BIRT Memory and Information Processing Battery)
- 2. Complex Figure test (from the BIRT Memory and Information Processing Battery)
- 3. CANTAB Stockings of Cambridge (SOC)
- 4. CANTAB Spatial Working Memory (SWM)
- 5. Telephone search dual task (from the Test of Everyday Attention

Secondary outcome measures

- 1. CANTAB Rapid Visual Information Processing Battery (RVIP)
- 2. CANTAB Spatial Span (SSP)
- 3. CANTAB Attentional Set-shifting (IDED)
- 4. Verbal Fluency /Controlled Oral Word Association Test (COWAT)
- 5. Cancellation task
- 6. Symptom Checklist 90R (SCL-90R)
- 7. Quality of Life in Epilepsy (QOLIE)
- 8. Liverpool Seizure Severity Scale (LSSS)
- 9. Vineland Adaptive Behavior Scales-II (VABS-II) (survey form)
- 10. Social Responsiveness Scale (SRS)
- 11. Social communication questionnaire (SCQ)

Overall study start date

01/12/2011

Completion date

06/08/2018

Eligibility

Key inclusion criteria

- 1. Definite TSC by current clinical criteria
- 2. Male or female aged 16 to 60 years

3. IQ over 60 by Wechsler Abbreviated Scales of Intelligence (WASI) and able to participate in direct neuropsychological tests

4. A score falling on, or below, the 5th percentile (approximately equivalent to -1.5 SD) in one or more of the primary outcome measures (updated 24/04/2019. Previously: Deficit of - 2 S.D. or more below normal population mean on a primary outcome measure)

5. Calculated glomerular filtration rate (GFR) > 60ml/min/1.73m2

6. International Normalized Ratio (INR) 1.5 or less (anticoagulation permitted if target INR on stable dose of warfarin or Low molecular weight (LMW) heparin for > 2 weeks at time of randomisation)

7. Adequate liver function as shown by: serum bilirubin less than or equal to 1.5 x upper limit of normal (ULN), alanine aminotranferease (ALT) and aspartate aminotransferase (AST) less than or equal to 2.5 x ULN

8. If sexually active - negative pregnancy test in females at the time of informed consent, contraception for males and pre-menopausal females on study

9. Seizure free or stable seizures as defined by no change in type of antiepileptic drugs (AEDs) in 6 months prior to recruitment. Doses of drugs may have been changed in the 6 months prior to recruitment

10. Negative Hepatitis B virus (HBV) DNA and Hepatitis C virus (HCV) RNA , polymerase chain reaction (PCR) testing at screening for patients with a positive history of risk factors and/or confirmation of prior HBV/HCV infection

11. All patients must be able to communicate well with the investigator, to understand and comply with the requirements of the study, understand and sign the written informed consent 12. Female patients of childbearing potential must be prepared to use two acceptable methods of contraception, (e.g. intra-uterine device plus condom, spermicidal gel plus condom, diaphragm plus condom, etc.), from the time of screening

Participant type(s)

Patient

Age group

Adult

Sex Both

Target number of participants 48

Total final enrolment

38

Key exclusion criteria

1. Prior treatment with an mTOR (mammalian target of rapamycin) inhibitor

2. Investigational agent <30 days prior to randomisation

3. Surgery in last 2 months

4. Previous brain neurosurgery with the exception of SEGA (sub-ependymal giant cell astrocytoma) removal surgery or radiosurgery 5 or more years ago (updated on 24/04/2019. Previously: Previous brain neurosurgery)

5. Significant haematological abnormality i.e. haemoglobin < 8g/dL, platelets <80,000/mm3, absolute neutrophil count < 1000/mm3)

6. Urine protein/creatinine >0.02g/mmol

7. Serum creatinine > 1.5 x ULN

8. Uncontrolled hyperlipidaemia (fasting cholesterol > 300mg/dL or >7.75 mmol/L and fasting triglycerides >2.5 x ULN, or diabetes with fasting serum glucose > 1.5 x ULN

9. History of myocardial infarction, angina or stroke related to atherosclerosis, or any other significant cardiac disease, human immunodeficiency virus (HIV) seropositivity, organ transplant, malignancy other than squamous or basal cell skin cancer

10. Lymphangioleiomyomatosis with forced expiratory volume in 1 second (FEV1) <70% of predicted, or any other restrictive pulmonary disease

11. Bleeding diathesis or on oral anti-vitamin K medication other than low dose warfarin

12. Pregnancy/lactation

- 13. Live vaccine required during trial
- 14. Use of strong inhibitor or inducer of CYP3AE except for anti epileptic drugs
- 15. Intercurrent infection at time of randomisation
- 16. Inability to complete study materials (outcome measures) in English
- 17. History of significant trauma-related cognitive deficit

18. Impairment of gastrointestinal function or gastrointestinal disease that may significantly alter the absorption of Everolimus (e.g. pancreatic insufficiency)

19. Known sensitivity to Everolimus or other Rapamycin analogues or to its excipients 20. Inability to attend scheduled visits

Date of first enrolment 31/12/2011

Date of final enrolment 27/10/2017

Locations

Countries of recruitment United Kingdom

Wales

Study participating centre Cardiff University Cardiff United Kingdom CF14 4XN

Sponsor information

Organisation Cardiff University (UK)

Sponsor details c/o Ms Kathy Pittard Davies Research and Commercial Division 7th Floor 30 - 36 Newport Road Cardiff Wales United Kingdom CF24 0DE

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Sponsor type University/education

Website http://www.cardiff.ac.uk/

ROR https://ror.org/03kk7td41

Funder(s)

Funder type Industry

Funder Name Novartis Pharmaceuticals UK Limited

Alternative Name(s) Novartis UK, NOVARTIS UK LIMITED

Funding Body Type Private sector organisation

Funding Body Subtype For-profit companies (industry)

Location United Kingdom

Results and Publications

Publication and dissemination plan Not provided at time of registration

Intention to publish date

Individual participant data (IPD) sharing plan

The datasets generated during the current study are available on request from ctrdatasamplerequests@cardiff.ac.uk

IPD sharing plan summary

Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
<u>Protocol article</u>	protocol	11/08/2016		Yes	No
<u>Thesis results</u>	version 1.0	19/07/2021	14/04/2022	No	No
<u>Statistical Analysis Plan</u>		05/07/2018	27/03/2023	No	No
Basic results		10/11/2021	28/03/2023	No	No
HRA research summary			28/06/2023	No	No