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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, neuro-cognitive 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

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Scientific

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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)

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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?
Protocol article	protocol	11/08/2016		Yes	No
Thesis results		19/07/2021	14/04/2022	No	No
Statistical Analysis Plan	version 1.0	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