Clinical trial results:
TRON: A randomised, double blind, placebo-controlled study of RAD001 (Everolimus) in the treatment of neurocognitive problems in tuberous sclerosis.

Summary

EudraCT number	2011-004854-25
Trial protocol	GB
Global end of trial date	06 August 2018

Results information

Result version number	v1 (current)
This version publication date	10 November 2021
First version publication date	10 November 2021

Trial information

Trial identification

Sponsor protocol code	SPON803-10

Additional study identifiers

ISRCTN number	ISRCTN09739757
ClinicalTrials.gov id (NCT number)	NCT01954693
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Cardiff University
Sponsor organisation address	30-36 Newport Road, Cardiff, United Kingdom, CF24 0DE
Public contact	Dr Cheney Drew, Cardiff University, 02920 687243, DrewC5@cardiff.ac.uk
Scientific contact	Prof Julian Sampson, Cardiff University, 02920 744050, Sampson@cardiff.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	18 July 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	06 August 2018
Global end of trial reached?	Yes
Global end of trial date	06 August 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to determine how effective Everolimus is compared to a placebo for recall memory (remembering events or information) and executive function (the ability to organise thoughts and activities, prioritise tasks, manage time and make decisions) in people with tuberous sclerosis over a 6 month period.

Protection of trial subjects:

Safety assessments were conducted to ensure ongoing health and wellness of participants as follows:

1) Physical and neurolgiocal examination at screening, baseline, 4, 12 and 24 week assessment points
2) Haematology, Serum Chemistry, spirometry and urine analysis were conducted at each timepoint.

Background therapy:

Tuberous Sclerosis is associated with a number of co-morbid conditions.

Evidence for comparator:

N/A, comparator used in this trial was placebo

Actual start date of recruitment	01 February 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: 38
Worldwide total number of subjects	38
EEA total number of subjects	38

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)	1
Adults (18-64 years)	37

From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This was a multi-centre Phase II trial. Recruitment took place in 3 sites: Cardiff, Belfast and Glasgow between 12/FEB/2012 and 06/AUG/2018.

Pre-assignment

Screening details:

Entry into the study was a two stage process: those likely to be eligible were offered a screening appointment (visit 1) at which fully informed written consent was obtained. A screening assessment including full medical history, current medications, physical examination, together with neurocognitive tests to confirm or refute eligibility.

Pre-assignment period milestones

Number of subjects started	67[1]
Intermediate milestone: Number of subjects	Screening: 67
Number of subjects completed	38

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Consent withdrawn by subject: 1
Reason: Number of subjects	Not eligible: 28

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Participants were screened for inlcusion in the pre-assignment period but not officially enrolled in the trial at this point.

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, Data analyst, Assessor

Blinding implementation details:

Randomisation data are kept strictly confidential, and accessible only to authorised personnel until database lock. The drug was supplied by Novartis as open label bulk supplies and sent to St Mary's Pharmaceutical Unit, Cardiff, for packaging and labeling. The participant’s unique identification number and allocation was to be double blinded, so neither the participant, clinician, research psychologist nor the statistician knew which treatment group the participant had been allocated to.

Arms

Are arms mutually exclusive?	Yes
Arm title	Everolimus

Arm description:

RAD001 (Everolimus) 5mg, administered for 6 months as two oral 2.5 mg tablets once daily.

Arm type	Experimental
Investigational medicinal product name	Everolimus
Investigational medicinal product code	EU/1/09/538/001
Other name	Afinitor
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Administration was 2.5mg tablets taken orally once a day. Starting dose of 5mg/day adjusted to achieve trough blood levels of 3-10ng/ml.

Arm title	Placebo

Arm description:

Matching placebo

Arm type	Placebo
Investigational medicinal product name	Placebo to match
Investigational medicinal product code	N/A
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Adminstration was 2 x 2.5mg tablets taken orally, once a day.

Number of subjects in period 1	Everolimus	Placebo
Started	25	13
Visit 3 (week 2)	24	12
Visit 4 (week 4)	24	12
Visit 5 (week 6)	24	12
Visit 6 (week 12)	24	12
Visit 7 (week 24)	24	12
Visit 8 (week 36)	23 [2]	12
Completed	24	12
Not completed	1	1
Consent withdrawn by subject	1	1

Notes:

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Participants were screened for inlcusion in the pre-assignment period but not officially enrolled in the trial at this point.

Baseline characteristics

Reporting groups	
Reporting group title	Everolimus
Reporting group description:	
RAD001 (Everolimus) 5mg, administered for 6 months as two oral 2.5 mg tablets once daily.	
Reporting group title	Placebo
Reporting group description:	
Matching placebo	

Reporting group values	Everolimus	Placebo	Total
Number of subjects	25	13	38
Age categorical Units: Subjects			
<50 years	21	10	31
>= 50 years	4	3	7
Gender categorical Units: Subjects			
Female	14	7	21
Male	11	6	17
IQ Level group Units: Subjects			
60-79	10	4	14
80 or more	15	9	24
Currently on anti-epilepsy drugs Units: Subjects			
No	9	4	13
Yes	16	9	25

End points

End points reporting groups

Reporting group title	Everolimus
Reporting group description:	
RAD001 (Everolimus) 5mg, administered for 6 months as two oral 2.5 mg tablets once daily.	
Reporting group title	Placebo
Reporting group description:	
Matching placebo	

Primary: Memory functioning

End point title	Memory functioning
End point description:	
The primary outcome for this study is memory functioning, with improved memory functioning classed as a one SD response on any of the following memory tests Complex Figure test and List Learning test from the BIRT Memory and Information Processing Battery, Spatial Working Memory (SWM) and Stockings of Cambridge (SOC) from the CANTAB, and Telephone search dual task from the Test of Everyday Attention.	
End point type	Primary
End point timeframe:	
Between baseline and Visit 7 (week 24 / 6 months)	

End point values	Everolimus	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	12		
Units: Improved memory functioning				
Yes - improved by one SD	20	9		
No - did not improve by one SD	3	3		

Statistical analyses

Statistical analysis title	Primary outcome
Statistical analysis description:	
The hypothesis for the primary analysis of the primary outcome in TRON was to observe a 15% learning effect in the placebo group and that an improvement of 35% or more in the Everolimus group would provide sufficient evidence for further investigation of Everolimus as a treatment for TAND. A one sample chi-squared test was used to determine whether the proportion of patients in the intervention group who improve their recall memory at 6 months by one SD was at least 0.35.	
Comparison groups	Placebo v Everolimus

Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	= 0.077 [2]
Method	Chi-squared

Notes:

[1] - A one-sample χ2 test for improvement to 95% (derived from adding the hypothesised 20-percentage point increase to the observed 75% improvement from baseline to 6 months in the Placebo arm) in the Everolimus arm provides a p-value of 0.077, implying no evidence to suggest that the observed proportion of 87.0% in Everolimus is different to the hypothesised 95%. This indicates no statistically significant difference between observing 95.0% or 87.0% improvement in the Everolimus arm given the data.

[2] - A one-sample χ2 test for improvement to 95% (derived from adding the hypothesised 20-percentage point increase to the observed 75% improvement from baseline to 6 months in the Placebo arm) in the Everolimus arm provides a p-value of 0.077.

Secondary: CANTAB Rapid Visual Information Processing - Standard score

End point title	CANTAB Rapid Visual Information Processing - Standard score

End point description:

End point type	Secondary

End point timeframe:

Baseline to 6 months follow-up

End point values	Everolimus	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	11		
Units: standard score				
number (not applicable)				
1SD improvement	1	0		

Statistical analyses

Statistical analysis title	1-sample chi-squared test

Statistical analysis description:

A one sample chi-squared test will be used to determine whether the proportion of patients in the Everolimus group who improve at six months by at least one SD is significantly greater than what is expected (the null hypothesis of equal proportions is rejected). A one sample chi-squared test will be used to determine whether the proportion of patients in the Ever

Comparison groups	Everolimus v Placebo
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	< 0.001
Method	1-sided chi-squared

Notes:

[3] - A one sample chi-squared test will be used to determine whether the proportion of patients in the Everolimus group who improve at six months by at least one SD is significantly greater than what is expected (the null hypothesis of equal proportions is rejected). A one sample chi-squared test will be used to determine whether the proportion of patients in the Ever

Secondary: CANTAB - Spatial span

End point title	CANTAB - Spatial span

End point description:

End point type	Secondary

End point timeframe:

Baseline to 6 months

End point values	Everolimus	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	12		
Units: Span length				
number (not applicable)				
1SD improvement	2	2		

Statistical analyses

Statistical analysis title	1 sample chi-squared

Statistical analysis description:

A one sample chi-squared test will be used to determine whether the proportion of patients in the Everolimus group who improve at six months by at least one SD is significantly greater than what is expected (the null hypothesis of equal proportions is rejected). A one sample chi-squared test will be used to determine whether the proportion of patients in the Ever

Comparison groups	Everolimus v Placebo
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	Chi-squared

Secondary: QOLIE - Seizure worry

End point title	QOLIE - Seizure worry

End point description:

End point type	Secondary

End point timeframe:

baseline to 6 months

End point values	Everolimus	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	11		
Units: score				
number (not applicable)				
1SD improvement	2	1		

Statistical analyses

Statistical analysis title	1-sample chi-square
Comparison groups	Everolimus v Placebo
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	other[4]
P-value	< 0.001
Method	Chi-squared

Notes:

[4] - A one sample chi-squared test will be used to determine whether the proportion of patients in the Everolimus group who improve at six months by at least one SD is significantly greater than what is expected (the null hypothesis of equal proportions is rejected).

Secondary: QOLIE- Overall Quality of Life

End point title	QOLIE- Overall Quality of Life

End point description:

End point type	Secondary

End point timeframe:

baseline to 6 months

End point values	Everolimus	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	11		
Units: score				
number (not applicable)				
1SD improvement	1	1		

Statistical analyses

Statistical analysis title	1 sample chi-squared
Comparison groups	Everolimus v Placebo

Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	other[5]
P-value	< 0.001
Method	Chi-squared

Notes:

[5] - A one sample chi-squared test will be used to determine whether the proportion of patients in the Everolimus group who improve at six months by at least one SD is significantly greater than what is expected (the null hypothesis of equal proportions is rejected).

Secondary: QOLIE -Fatigue

End point title	QOLIE -Fatigue

End point description:

End point type	Secondary

End point timeframe:

baseline to 6 months

End point values	Everolimus	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	11		
Units: score				
number (not applicable)				
1SD improvement	2	1		

Statistical analyses

Statistical analysis title	1 sample chi-squared
Comparison groups	Everolimus v Placebo
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	other[6]
P-value	< 0.001
Method	Chi-squared

Notes:

[6] - A one sample chi-squared test was used to determine whether the proportion of patients in the Everolimus group who improve at six months by at least one SD is significantly greater than what is expected (the null hypothesis of equal proportions is rejected).

Secondary: QOLIE - Cognitive functioning

End point title	QOLIE - Cognitive functioning

End point description:

End point type	Secondary

End point timeframe:

Baseline to 6 months

End point values	Everolimus	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	11		
Units: score				
number (not applicable)				
1 SD improvement	4	2		

Statistical analyses

Statistical analysis title	1-sample chi-squared
Comparison groups	Everolimus v Placebo
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	other[7]
P-value	= 0.003
Method	Chi-squared

Notes:

[7] - A one sample chi-squared test will be used to determine whether the proportion of patients in the Everolimus group who improve at six months by at least one SD is significantly greater than what is expected (the null hypothesis of equal proportions is rejected).

Secondary: QOLIE - Medication effects

End point title	QOLIE - Medication effects

End point description:

End point type	Secondary

End point timeframe:

Baseline to 6 months

End point values	Everolimus	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	11		
Units: score				
number (not applicable)				
1SD improvement	3	1		

Statistical analyses

Statistical analysis title	1-sample chi-squared
Comparison groups	Everolimus v Placebo

Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	other[8]
P-value	< 0.001
Method	Chi-squared

Notes:

[8] - A one sample chi-squared test will be used to determine whether the proportion of patients in the Everolimus group who improve at six months by at least one SD is significantly greater than what is expected (the null hypothesis of equal proportions is rejected).

Secondary: QOLIE - Social functioning

End point title	QOLIE - Social functioning

End point description:

End point type	Secondary

End point timeframe:

Baseline to 6 months

End point values	Everolimus	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	11		
Units: score				
number (not applicable)				
1SD improvement	4	1		

Statistical analyses

Statistical analysis title	1-sample chi-squared
Comparison groups	Everolimus v Placebo
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	other[9]
P-value	= 0.003
Method	Chi-squared

Notes:

[9] - A one sample chi-squared test will be used to determine whether the proportion of patients in the Everolimus group who improve at six months by at least one SD is significantly greater than what is expected (the null hypothesis of equal proportions is rejected).

Secondary: QOLIE - Overall score

End point title	QOLIE - Overall score

End point description:

End point type	Secondary

End point timeframe:

Baseline to 6 months

End point values	Everolimus	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	11		
Units: score				
number (not applicable)				
1SD improvement	3	0		

Statistical analyses

Statistical analysis title	1-sample chi-squared
Comparison groups	Everolimus v Placebo
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	other[10]
P-value	= 0.001
Method	Chi-squared

Notes:

[10] - A one sample chi-squared test will be used to determine whether the proportion of patients in the Everolimus group who improve at six months by at least one SD is significantly greater than what is expected (the null hypothesis of equal proportions is rejected).

Secondary: Symptoms Checklist 90 (SCL-90R) - Somatization

End point title	Symptoms Checklist 90 (SCL-90R) - Somatization

End point description:

End point type	Secondary

End point timeframe:

Baseline to 6 months

End point values	Everolimus	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	12		
Units: score				
number (not applicable)				
1SD improvement	3	2		

Statistical analyses

Statistical analysis title	1-sample chi-squared
Comparison groups	Everolimus v Placebo

Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	other[11]
P-value	= 0.001
Method	Chi-squared

Notes:

[11] - A one sample chi-squared test will be used to determine whether the proportion of patients in the Everolimus group who improve at six months by at least one SD is significantly greater than what is expected (the null hypothesis of equal proportions is rejected).

Secondary: SCL-90R - Obsessive-Compulsive

End point title	SCL-90R - Obsessive-Compulsive

End point description:

End point type	Secondary

End point timeframe:

Baseline to 6 months

End point values	Everolimus	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	11		
Units: score				
number (not applicable)				
1SD improvement	1	1		

Statistical analyses

Statistical analysis title	1-sample chi-squared
Comparison groups	Everolimus v Placebo
Number of subjects included in analysis	29
Analysis specification	Pre-specified
Analysis type	other[12]
P-value	< 0.001
Method	Chi-squared

Notes:

[12] - A one sample chi-squared test will be used to determine whether the proportion of patients in the Everolimus group who improve at six months by at least one SD is significantly greater than what is expected (the null hypothesis of equal proportions is rejected).

Statistical analysis title	1-sample chi-squared
Comparison groups	Everolimus v Placebo
Number of subjects included in analysis	29
Analysis specification	Pre-specified
Analysis type	other[13]
P-value	< 0.001
Method	Chi-squared

Notes:

[13] - A one sample chi-squared test will be used to determine whether the proportion of patients in the Everolimus group who improve at six months by at least one SD is significantly greater than what is expected (the null hypothesis of equal proportions is rejected).

Secondary: SCL-90R - Interpersonal Sensitivity

End point title	SCL-90R - Interpersonal Sensitivity

End point description:

End point type	Secondary

End point timeframe:

Baseline to 6 months

End point values	Everolimus	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	10		
Units: score				
number (not applicable)				
1SD improvement	2	0		

Statistical analyses

Statistical analysis title	1-sample chi-squared
Comparison groups	Everolimus v Placebo
Number of subjects included in analysis	29
Analysis specification	Pre-specified
Analysis type	other[14]
P-value	= 0.001
Method	Chi-squared

Notes:

[14] - A one sample chi-squared test will be used to determine whether the proportion of patients in the Everolimus group who improve at six months by at least one SD is significantly greater than what is expected (the null hypothesis of equal proportions is rejected).

Secondary: SCL-90R - Depression

End point title	SCL-90R - Depression

End point description:

End point type	Secondary

End point timeframe:

Baseline to 6 months

End point values	Everolimus	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	11		
Units: score				
number (not applicable)				
1SD improvement	1	1		

Statistical analyses

Statistical analysis title	1-sample chi-squared
Comparison groups	Everolimus v Placebo
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	other[15]
P-value	< 0.001
Method	Chi-squared

Notes:

[15] - A one sample chi-squared test will be used to determine whether the proportion of patients in the Everolimus group who improve at six months by at least one SD is significantly greater than what is expected (the null hypothesis of equal proportions is rejected).

Secondary: SCL-90R - Anxiety

End point title	SCL-90R - Anxiety

End point description:

End point type	Secondary

End point timeframe:

Baseline to 6 months

End point values	Everolimus	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	11		
Units: score				
number (not applicable)				
1SD improvement	2	3		

Statistical analyses

Statistical analysis title	1-sample chi-squared
Comparison groups	Everolimus v Placebo

Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	other[16]
P-value	< 0.001
Method	Chi-squared

Notes:

[16] - A one sample chi-squared test will be used to determine whether the proportion of patients in the Everolimus group who improve at six months by at least one SD is significantly greater than what is expected (the null hypothesis of equal proportions is rejected).

Secondary: SCL-90R - Hostility

End point title	SCL-90R - Hostility

End point description:

End point type	Secondary

End point timeframe:

Baseline to 6 months

End point values	Everolimus	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	11		
Units: score				
number (not applicable)				
1SD improvement	3	1		

Statistical analyses

Statistical analysis title	1SD improvement
Comparison groups	Everolimus v Placebo
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	other[17]
P-value	= 0.001
Method	Chi-squared

Notes:

[17] - A one sample chi-squared test will be used to determine whether the proportion of patients in the Everolimus group who improve at six months by at least one SD is significantly greater than what is expected (the null hypothesis of equal proportions is rejected).

Secondary: SCL-90R - Phobic Anxiety

End point title	SCL-90R - Phobic Anxiety

End point description:

End point type	Secondary

End point timeframe:

Baseline to 6 months

End point values	Everolimus	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	11		
Units: score				
number (not applicable)				
1SD improvement	1	0		

Statistical analyses

Statistical analysis title	1-sample chi-squared
Comparison groups	Everolimus v Placebo
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	other[18]
P-value	= 0.001
Method	Chi-squared

Notes:

[18] - A one sample chi-squared test will be used to determine whether the proportion of patients in the Everolimus group who improve at six months by at least one SD is significantly greater than what is expected (the null hypothesis of equal proportions is rejected).

Secondary: SCL-90R - Paranoid Ideation

End point title	SCL-90R - Paranoid Ideation

End point description:

End point type	Secondary

End point timeframe:

Baseline to 6 months

End point values	Everolimus	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	11		
Units: score				
number (not applicable)				
1SD improvement	1	0		

Statistical analyses

Statistical analysis title	1-sample chi-squared
Comparison groups	Everolimus v Placebo

Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	other[19]
P-value	= 0.001
Method	Chi-squared

Notes:

[19] - A one sample chi-squared test will be used to determine whether the proportion of patients in the Everolimus group who improve at six months by at least one SD is significantly greater than what is expected (the null hypothesis of equal proportions is rejected).

Secondary: SCL-90R - Psychoticism

End point title	SCL-90R - Psychoticism

End point description:

End point type	Secondary

End point timeframe:

Baseline to 6 months

End point values	Everolimus	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	10		
Units: score				
number (not applicable)				
1SD improvement	1	1		

Statistical analyses

Statistical analysis title	1-sample chi-squared
Comparison groups	Everolimus v Placebo
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	other[20]
P-value	< 0.001
Method	Chi-squared

Notes:

[20] - A one sample chi-squared test will be used to determine whether the proportion of patients in the Everolimus group who improve at six months by at least one SD is significantly greater than what is expected (the null hypothesis of equal proportions is rejected).

Secondary: SCL-90R - Global Severity Index

End point title	SCL-90R - Global Severity Index

End point description:

End point type	Secondary

End point timeframe:

Baseline to 6 months

End point values	Everolimus	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	8		
Units: score				
number (not applicable)				
1SD improvement	1	0		

Statistical analyses

Statistical analysis title	1-sample chi-squared
Comparison groups	Everolimus v Placebo
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority[21]
P-value	< 0.001
Method	Chi-squared

Notes:

[21] - A one sample chi-squared test will be used to determine whether the proportion of patients in the Everolimus group who improve at six months by at least one SD is significantly greater than what is expected (the null hypothesis of equal proportions is rejected).

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events were monitored from baseline to study end and AEs ongoing on completion of the study were followed up as clinically indicated.

Adverse event reporting additional description:

Patients entered into the study were encouraged from the outset to contact the clinical team at the time of an adverse event occurring. In addition, at each visit, AEs that might have occurred since the previous visit were reported.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.1

Reporting groups

Reporting group title	Everolimus

Reporting group description:

Includes participants randomsied to receive Everolimus

Reporting group title	Placebo

Reporting group description:

This includes all participants randomised to the placebo group

Serious adverse events	Everolimus	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 25 (12.00%)	2 / 13 (15.38%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Nervous system disorders			
Seizure cluster	Additional description: Increased seiure frequency requiring hopitilisation		
subjects affected / exposed	0 / 25 (0.00%)	1 / 13 (7.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Suicidal ideation	Additional description: Recurrence of previous suicidal ideation prior to participation in trial.		
subjects affected / exposed	3 / 25 (12.00%)	1 / 13 (7.69%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Everolimus	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	21 / 25 (84.00%)	8 / 13 (61.54%)	
Vascular disorders			
epistaxis			
subjects affected / exposed	0 / 25 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Surgical and medical procedures			
Weight loss diet			
subjects affected / exposed	1 / 25 (4.00%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Oedema extremities			
subjects affected / exposed	1 / 25 (4.00%)	1 / 13 (7.69%)	
occurrences (all)	1	1	
Flu like symptoms			
subjects affected / exposed	6 / 25 (24.00%)	0 / 13 (0.00%)	
occurrences (all)	9	0	
Respiratory, thoracic and mediastinal disorders			
Respiratory tract infection			
subjects affected / exposed	7 / 25 (28.00%)	4 / 13 (30.77%)	
occurrences (all)	6	10	
Psychiatric disorders			
Agitation			
subjects affected / exposed	1 / 25 (4.00%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Investigations			
Elevated Creatine Phosphokinase			
subjects affected / exposed	0 / 25 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
High liver enzymes			
subjects affected / exposed	1 / 25 (4.00%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
High IMP level			
subjects affected / exposed	1 / 25 (4.00%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Injury, poisoning and procedural complications			

Burns first degree			
subjects affected / exposed	1 / 25 (4.00%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 25 (8.00%)	2 / 13 (15.38%)	
occurrences (all)	3	2	
Seizure			
subjects affected / exposed	2 / 25 (8.00%)	0 / 13 (0.00%)	
occurrences (all)	2	0	
Dizziness			
subjects affected / exposed	1 / 25 (4.00%)	2 / 13 (15.38%)	
occurrences (all)	1	2	
Dysgeusia			
subjects affected / exposed	1 / 25 (4.00%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
hypersomnolence			
subjects affected / exposed	1 / 25 (4.00%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
drop attacks	Additional description: Increase in frequency		
subjects affected / exposed	1 / 25 (4.00%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 25 (4.00%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Neutropenia			
subjects affected / exposed	2 / 25 (8.00%)	0 / 13 (0.00%)	
occurrences (all)	3	0	
Eye disorders			
blurred vision			
subjects affected / exposed	1 / 25 (4.00%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Oral Mucositis			
subjects affected / exposed	13 / 25 (52.00%)	2 / 13 (15.38%)	
occurrences (all)	32	2	

Diarrhoea			
subjects affected / exposed	3 / 25 (12.00%)	2 / 13 (15.38%)	
occurrences (all)	3	2	
Inguinal hernia			
subjects affected / exposed	1 / 25 (4.00%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Toothache			
subjects affected / exposed	3 / 25 (12.00%)	0 / 13 (0.00%)	
occurrences (all)	4	0	
Skin and subcutaneous tissue disorders			
Eczema			
subjects affected / exposed	1 / 25 (4.00%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Hyperhidrosis			
subjects affected / exposed	1 / 25 (4.00%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
skin rash			
subjects affected / exposed	3 / 25 (12.00%)	1 / 13 (7.69%)	
occurrences (all)	4	1	
Renal and urinary disorders			
Urinary incontinence			
subjects affected / exposed	1 / 25 (4.00%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Proteinuria			
subjects affected / exposed	1 / 25 (4.00%)	1 / 13 (7.69%)	
occurrences (all)	1	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 25 (8.00%)	0 / 13 (0.00%)	
occurrences (all)	2	0	
Back pain			
subjects affected / exposed	1 / 25 (4.00%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Chest wall pain			
subjects affected / exposed	1 / 25 (4.00%)	0 / 13 (0.00%)	
occurrences (all)	1	0	

Infections and infestations			
Skin infection			
subjects affected / exposed	5 / 25 (20.00%)	0 / 13 (0.00%)	
occurrences (all)	6	0	
Otitis externa			
subjects affected / exposed	1 / 25 (4.00%)	0 / 13 (0.00%)	
occurrences (all)	2	0	
Paronychia			
subjects affected / exposed	1 / 25 (4.00%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Urinary tract infection			
subjects affected / exposed	1 / 25 (4.00%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Hypophosphatemia			
subjects affected / exposed	1 / 25 (4.00%)	1 / 13 (7.69%)	
occurrences (all)	1	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 October 2011	• Postponement of appointments in event of seizures (p40, 7.0) • All patients to have Hepatitis B and C screening prior to randomization (p29; 5.1.1, p41; 7.1). Any positive results go to GP for further confirmatory tests. • Patients will not be tested for HIV but will be excluded if known to be HIV seropositive (p30; 5.1.2)
20 December 2011	• Exclusion criterion regarding potent inhibitors of CYP3A4 • Development Safety Update Reports have now replaced Annual Safety Reports. • MHRA must approve all amendments to protocol before implementation and notified at the time an Urgent Safety Measure is taken
01 February 2012	• Cardiff will deliver the packed open labeled drug and placebo to the pharmacy at the University Hospital of Wales for dispensing • Randomisation details • Treatment blinding details • Unblinding section • The SRS listed is now the SRS-A • In the event of a positive result, participants will be referred for appropriate counselling and further management via their GP. • Dipstick Urinalysis will also be carried out at weeks 2, 6, 36 • SAEs to be reported to Novartis within one business day. Unblinding will be carried out by SEWTU before the SAE is passed to Novartis • Inclusion of Nominated person details • 'EDTA anticoagulated tube marked with patient name, hospital and trial number, date/time of sample collection' – changed to PID/DOB and initials
04 October 2012	• Trial Steering Committee now referred to as Study Steering Committee (SSC) to avoid confusion with Tuberous Sclerosis Complex (TSC) • Addition of the NART premorbid test as a secondary outcome measure • Addition of Co-investigators • Alteration to dosing modifications in case of toxicities to bring in line with the SmPC. Specifically with regard to Grade 2&3 • Out dated reference to ECG and electrocardiogram were removed
02 February 2013	• Inclusion of Co investigators details to TRON • Substantial Amendment: Imaging study • Inclusion of Brain DTI MR scan in assessment schedule • Inclusion of Brain DTI MR Scan on Visit 2 & Visit 7 in TRON flow chart
15 February 2013	Addition of detail on informed consent. The SRS-A will no longer be undertaken at visit 4, the VABS-2 will no longer be undertaken at visit 6. (see table 2)
26 February 2013	• Revision of data analysis in sub-study following Novartis review
07 November 2013	• Addition of new wording for SAE section • Change of Trial Manager

06 May 2014	• Amendment of exclusion criteria for Previous Brain Neurosurgery so those who have had SEGA (sub-ependymal giant cell astrocytoma) surgery or radiosurgery over 5 years ago are now eligible
25 September 2014	• Removal of the Social Responsiveness Scale - Adult, and the Social Communication Questionnaire (SCQ) at 3 month interview
05 January 2015	• One eligibility criteria has been altered as it was felt to be overly stringent. Previously, individuals were required to have a score of -2 standard deviations (SD) on any one of the primary outcomes in order to be eligible to take part. This has been adjusted to approximately -1.5 SD. • Entry criteria regarding kidney function has also been updated in light of new evidence. • Wording in relation to IMP dispensing has been refined in order to make it more clear as to when and how participants might be prescribed an increase in dose.
06 August 2015	• Section 1.2.6 addition of new marketing authorization for Everolimus for the treatment of renal angiomyolipoma in TSC • Section 7.2 Addition of the need for fasted bloods to be repeated if it was not possible to do them at a planned study visit. • Section 7.4 Addition of provision for blood to be drawn and submitted for pharmacokinetic analysis by participant's GP • Section 9.2 update for procedures for receiving safety information from Novartis.
02 March 2016	• Addition to text (where relevant) of the new research sites at Belfast City Hospital and Queen Elizabeth University Hospital, Glasgow and removal of specific references to Cardiff and/or University Hos[ital Wales as the only research site. • Section 6.2: Change to the process of Patient Identification Number allocation from assignation the point of consent to assignation at the point of confirmation of attendance to eligibility assessment appointment. • Section 6.3: Addition of process for randomization for new sites

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Different versions of the TEA were used between baseline and primary endpoint. These are scored differently, so direct comparison is difficult. Participants entered on the basis of the TEA were excluded in a sensitivity analysis.

Notes: