Clinical trial results:
Phase II triple blind placebo controlled RCT of simvastatin treatment for autism in young children with Neurofibromatosis Type 1

Summary

EudraCT number	2012-005742-38
Trial protocol	GB
Global end of trial date	30 November 2015

Results information

Result version number	v1 (current)
This version publication date	13 May 2020
First version publication date	13 May 2020

Trial information

Trial identification

Sponsor protocol code	R02145

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	REC reference: 13/NW/0111

Notes:

Sponsors

Sponsor organisation name	Manchester University NHS Foundation Trust
Sponsor organisation address	Oxford Road, Manchester, United Kingdom,
Public contact	Lynne Webster, Manchester University NHS Foundation Trust, +44 01612764125, research.sponsor@mft.nhs.uk
Scientific contact	Lynne Webster, Manchester University NHS Foundation Trust, +44 01612764125, research.sponsor@mft.nhs.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	30 November 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 November 2015
Global end of trial reached?	Yes
Global end of trial date	30 November 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The overall research aim is to determine whether treatment with statins improves the ASD phenotype in children with NF1 autism. This aim of this study is to test:
-Acceptability and feasibility of involvement for families of children with NF1 ASD
-The feasibility and acceptability of the assessment protocol
-Treatment effects on intermediate and endpoint behavioural phenotype measures and imaging parameters

The hypothesis is that treatment with statins in young children with NF1 autism will be:
-Feasible, safe and acceptable to families
-Associated with signals of change in brain imaging parameters
-Associated with signals of change in autism and other behavioural symptoms

Protection of trial subjects:

Risks and burdens identified to the participants include the burden of travel to research site, possible distress caused by blood tests and brain scan and the risk associated with the treatment. The protocol has been designed to reduce these risks as following:

Burden of travel: The study has been designed with careful consideration of the burden on the participants. The trial team has sought to keep the burden of the treatment visits and intervention to the absolute minimum possible whilst at the same time ensuring safety of participants. The initial screening will be via postal questionnaire and the followup at 16 weeks via a telephone call in order to reduce the number of participant visits.

Possible distress due to blood tests and brain scan: Experienced paediatric nurses will carry out blood tests. Play therapist will be used to help explain the procedures to the children in a developmentally appropriate way.

Risks associated with medication: Stringent monitoring of adverse effects of medication will be carried out during the course of treatment. This will include both verbal enquiry as well as blood tests. The statin expert on the team (AM) has extensive clinical experience of the use of statins in very young children. He will be available for advice and for monitoring the results of the blood tests.

Confidentiality; The research team will have access to person identifiable information only when they receive the screening pack back from parents. No person identifiable information will be used in any publication/advertisement of the trial. Parents will be explained that all the assessments will be confidential and that confidentiality will be maintained at all times other than when the participant is identified as being at serious risk (such as child protection issues). In such cases, the information will be discussed with the CI and anonymously discussed with the child protection lead nurse at MFT.

Background therapy:

N/A

Evidence for comparator: -

Actual start date of recruitment	30 September 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 34
Worldwide total number of subjects	34
EEA total number of subjects	34

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)	34
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment start date: 30/09/2013
Recruitment end date: 30/11/2015
Territory: UK only

Pre-assignment

Screening details: -

Pre-assignment period milestones

Number of subjects started	34
Number of subjects completed	30

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Consent withdrawn by subject: 2
Reason: Number of subjects	Not NF1 diagnosis: 2

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description: -

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral suspension
Routes of administration	Oral use

Dosage and administration details:

N/A - placebo

Arm title	Simvastatin

Arm description:

Intervention arm

Arm type	Experimental
Investigational medicinal product name	Simvastatin
Investigational medicinal product code	PL 00427/0146
Other name	
Pharmaceutical forms	Oral suspension
Routes of administration	Oral use

Dosage and administration details:

0.5mg/kg/dau in a single dose or placebo for 4 weeks. Those showing no significant adverse events after 4 weeks, will be escalated to a dose of 1mg/kg/day to a maximum of 30 mg/day in a single daily dose for a further 8 weeks

Number of subjects in period 1[1]	Placebo	Simvastatin
Started	16	14
Completed	15	11
Not completed	1	3
Lost to follow-up	1	2
Consent withdrawn	-	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Four participants were withdrawn from the trial prior to randomisation: two withdrew and two proved not to have NF1 diagnosis.

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description: -	
Reporting group title	Simvastatin
Reporting group description:	
Intervention arm	

Reporting group values	Placebo	Simvastatin	Total
Number of subjects	16	14	30
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	16	14	30
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	8.28	7.90	
standard deviation	± 1.76	± 1.90	-
Gender categorical Units: Subjects			
Female	2	4	6
Male	14	10	24
Mutation Units: Subjects			
Inherited	10	3	13
De novo	5	11	16
Not recorded	1	0	1
Riccardi Scale Units: Subjects			
one	3	4	7
two	12	5	17
three	0	4	4
four	1	1	2
Parent-Nominated Target Symptoms: Hyperactivity Units: Subjects			
Yes	6	7	13
No	10	7	17
Parent-nominated target symptoms: Agression			

Units: Subjects			
Yes	6	7	13
No	10	7	17
Parent-nominated target symptoms: Social inappropriateness Units: Subjects			
Yes	9	9	18
No	7	5	12
Parent-nominated target symptoms: Problems with communication Units: Subjects			
Yes	3	2	5
No	13	12	25
Parent-nominated target symptoms: Inflexibility/obsessionality Units: Subjects			
Yes	7	2	9
No	9	12	21
Parent-nominated target characteristics: Learning problems Units: Subjects			
Yes	1	2	3
No	15	12	27
Weight Units: kg			
arithmetic mean	29.85	25.76	
standard deviation	± 8.51	± 6.08	-
Social Responsiveness Scale: T Score Units: Scale			
arithmetic mean	83.06	82.93	
standard deviation	± 7.58	± 8.67	-
Social interaction			
Autism Diagnostic interview scale: Total A			
Units: Scale			
arithmetic mean	18.88	16.29	
standard deviation	± 5.08	± 5.08	-
Social communication			
Autism diagnostic interview: Total B			
Units: Scale			
arithmetic mean	14.19	14.00	
standard deviation	± 4.37	± 4.02	-
Restricted repetitive behaviours			
Autism diagnostic interview: Total C			
Units: Scale			
arithmetic mean	5.88	5.93	
standard deviation	± 2.78	± 2.64	-
ADOS: Social affect Units: scale			
arithmetic mean	10.13	9.29	
standard deviation	± 3.26	± 3.24	-
ADOS: RRB Units: Scale			
arithmetic mean	1.88	2.14	

standard deviation	± 1.63	± 1.74	-
ADOS: Total			
Units: Score			
arithmetic mean	12.00	11.57	
standard deviation	± 3.81	± 3.96	-
WASI verbal IQ			
n= 26			
Units: score			
arithmetic mean	81.57	90.00	
standard deviation	± 12.99	± 11.24	-
Aberrant Behaviour Checklist: Irritability			
Units: Score			
arithmetic mean	19.40	24.21	
standard deviation	± 10.38	± 9.36	-
Aberrant Behaviour Checklist: Lethargy			
Units: Score			
arithmetic mean	14.20	16.08	
standard deviation	± 8.36	± 6.85	-
Aberrant behaviour checklist: Stereotypy			
Units: Score			
arithmetic mean	4.87	7.29	
standard deviation	± 3.56	± 5.04	-
Aberrant Behaviour Checklist: Hyperactivity			
Units: Score			
arithmetic mean	24.07	30.21	
standard deviation	± 13.04	± 8.75	-
Aberrant Behaviour Checklist: Inappropriate speech			
Units: Score			
arithmetic mean	5.93	7.43	
standard deviation	± 3.15	± 3.61	-
Clinical Global Impression: Severity of illness			
Units: Score			
arithmetic mean	3.88	3.57	
standard deviation	± 0.885	± 0.646	-
Conners 3 Parent Rating Scale: Inattention			
Units: Score			
arithmetic mean	79.73	80.71	
standard deviation	± 12.13	± 9.36	-
Conners 3 Parent Rating Scale: Hyperactivity			
Units: score			
arithmetic mean	71.87	81.14	
standard deviation	± 14.75	± 8.88	-

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description: -	
Reporting group title	Simvastatin
Reporting group description:	
Intervention arm	

Primary: Parent defined target symptoms (PDTS)

End point title	Parent defined target symptoms (PDTS)[1]
End point description:	
End point type	Primary
End point timeframe:	
12 weeks	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: These are descriptive endpoints only

End point values	Placebo	Simvastatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	12		
Units: Scale				
arithmetic mean (standard deviation)	3.516 (± 1.768)	3.250 (± 1.684)		

Statistical analyses

No statistical analyses for this end point

Primary: Completed imaging assessments

End point title	Completed imaging assessments[2]
End point description:	
End point type	Primary
End point timeframe:	
Study duraton	

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: These are descriptive endpoints only

End point values	Placebo	Simvastatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	14		
Units: Subjects				
Yes	15	11		
No	1	3		

Statistical analyses

No statistical analyses for this end point

Secondary: ABC: Irritability

End point title	ABC: Irritability
End point description: Individual components of the ABC scale	
End point type	Secondary
End point timeframe: 12 weeks	

End point values	Placebo	Simvastatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	13		
Units: Scale				
arithmetic mean (standard deviation)	16.40 (± 10.82)	22.31 (± 12.14)		

Statistical analyses

Statistical analysis title	ABC: Irritabililty
Comparison groups	Placebo v Simvastatin
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Mean difference (final values)
Point estimate	1.66
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.61
upper limit	7.93
Variability estimate	Standard error of the mean
Dispersion value	3.2

Secondary: ABC: Lethargy	
End point title	ABC: Lethargy
End point description: Component of the ABC scale	
End point type	Secondary
End point timeframe: 12 weeks	

End point values	Placebo	Simvastatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	12		
Units: Scale				
arithmetic mean (standard deviation)	10.53 (± 9.61)	15.25 (± 10.30)		

Statistical analyses

Statistical analysis title	ABC: Lethargy
Comparison groups	Placebo v Simvastatin
Number of subjects included in analysis	27
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Mean difference (final values)
Point estimate	3.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.09
upper limit	11.28
Variability estimate	Standard error of the mean
Dispersion value	3.92

Secondary: ABC: Stereotypy	
End point title	ABC: Stereotypy
End point description:	
End point type	Secondary
End point timeframe: 12 weeks	

End point values	Placebo	Simvastatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	13		
Units: Scale				
arithmetic mean (standard deviation)	3.93 (± 3.63)	7.77 (± 5.83)		

Statistical analyses

Statistical analysis title	ABC: Stereotypy
Comparison groups	Placebo v Simvastatin
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Mean difference (final values)
Point estimate	1.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.98
upper limit	4.2
Variability estimate	Standard error of the mean
Dispersion value	1.32

Secondary: ABC: Hyperactivity

End point title	ABC: Hyperactivity

End point description:

End point type	Secondary

End point timeframe:

12 weeks

End point values	Placebo	Simvastatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	11		
Units: Scale				
arithmetic mean (standard deviation)	19.13 (± 13.17)	28.77 (± 12.83)		

Statistical analyses

Statistical analysis title	ABC: Hyperactivity
Comparison groups	Placebo v Simvastatin
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	3.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.28
upper limit	11.01
Variability estimate	Standard error of the mean
Dispersion value	3.65

Secondary: ABC: Inappropriate speech	
End point title	ABC: Inappropriate speech
End point description:	
End point type	Secondary
End point timeframe:	
12 weeks	

End point values	Placebo	Simvastatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	11		
Units: Scale				
arithmetic mean (standard deviation)	4.80 (± 2.54)	7.15 (± 3.31)		

Statistical analyses

Statistical analysis title	ABC: Inappropriate speech
Comparison groups	Placebo v Simvastatin

Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Mean difference (final values)
Point estimate	1.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1
upper limit	3.63
Variability estimate	Standard error of the mean
Dispersion value	0.95

Secondary: 25% reduction irritability scale

End point title	25% reduction irritability scale

End point description:

End point type	Secondary

End point timeframe:

12 weeks

End point values	Placebo	Simvastatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	13		
Units: Subjects				
yes	5	6		

Statistical analyses

No statistical analyses for this end point

Secondary: Conners: Inattention

End point title	Conners: Inattention

End point description:

End point type	Secondary

End point timeframe:

12 weeks

End point values	Placebo	Simvastatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	13		
Units: Scale				
arithmetic mean (standard deviation)	74.53 (± 14.16)	80.38 (± 10.08)		

Statistical analyses

Statistical analysis title	Conners: Inattention
Comparison groups	Placebo v Simvastatin
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	other
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	5.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.96
upper limit	11.61
Variability estimate	Standard error of the mean
Dispersion value	3.21

Secondary: Conners: Hyperactivity

End point title	Conners: Hyperactivity

End point description:

End point type	Secondary

End point timeframe:

12 Weeks

End point values	Placebo	Simvastatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	13		
Units: Scale				
arithmetic mean (standard deviation)	69.40 (± 17.12)	78.31 (± 13.51)		

Statistical analyses

Statistical analysis title	Conners: Hyperactivity
Comparison groups	Placebo v Simvastatin
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Mean difference (final values)
Point estimate	-0.98
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.09
upper limit	6.13
Variability estimate	Standard error of the mean
Dispersion value	3.63

Secondary: Conners: Learning problems	
End point title	Conners: Learning problems
End point description:	
End point type	Secondary
End point timeframe:	
12 weeks	

End point values	Placebo	Simvastatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	13		
Units: Scale				
arithmetic mean (standard deviation)	65.40 (± 12.91)	73.69 (± 15.71)		

Statistical analyses

Statistical analysis title	Conners: Learning problems
Comparison groups	Placebo v Simvastatin
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Mean difference (final values)
Point estimate	1.59

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.13
upper limit	5.3
Variability estimate	Standard error of the mean
Dispersion value	1.89

Secondary: Conners: Executive function

End point title	Conners: Executive function
End point description:	
End point type	Secondary
End point timeframe:	
12 weeks	

End point values	Placebo	Simvastatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	13		
Units: Scale				
arithmetic mean (standard deviation)	68.20 (± 16.24)	76.00 (± 11.66)		

Statistical analyses

Statistical analysis title	Conners: Executive function
Comparison groups	Placebo v Simvastatin
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Mean difference (final values)
Point estimate	4.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.51
upper limit	10.59
Variability estimate	Standard error of the mean
Dispersion value	3.34

Secondary: Conners: Aggression

End point title	Conners: Aggression

End point description:

End point type	Secondary

End point timeframe:

12 weeks

End point values	Placebo	Simvastatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	13		
Units: Scale				
arithmetic mean (standard deviation)	68.40 (± 20.86)	72.77 (± 17.09)		

Statistical analyses

Statistical analysis title	Conners: Aggression
Comparison groups	Placebo v Simvastatin
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Mean difference (final values)
Point estimate	-0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.05
upper limit	10.96
Variability estimate	Standard error of the mean
Dispersion value	5.61

Secondary: Conners: Peer relations

End point title	Conners: Peer relations

End point description:

End point type	Secondary

End point timeframe:

12 weeks

End point values	Placebo	Simvastatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	13		
Units: Scale				
arithmetic mean (standard deviation)	83.89 (± 11.53)	86.08 (± 8.73)		

Statistical analyses

Statistical analysis title	Conners: Peer relations
Comparison groups	Placebo v Simvastatin
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Mean difference (final values)
Point estimate	1.38
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.45
upper limit	7.21
Variability estimate	Standard error of the mean
Dispersion value	2.97

Secondary: Responders

End point title	Responders
End point description:	
End point type	Secondary
End point timeframe:	
12 weeks	

End point values	Placebo	Simvastatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	12		
Units: Subjects				
PDTS score < 3	2	5		

Statistical analyses

No statistical analyses for this end point

Secondary: Global improvement

End point title	Global improvement

End point description:

End point type	Secondary

End point timeframe:

12 weeks

End point values	Placebo	Simvastatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	12		
Units: Scale				
arithmetic mean (standard deviation)	3.57 (± 0.852)	3.00 (± 0.739)		

Statistical analyses

No statistical analyses for this end point

Secondary: Treatment responder

End point title	Treatment responder

End point description:

End point type	Secondary

End point timeframe:

12 weeks

End point values	Placebo	Simvastatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	14		
Units: Subjects				
Yes	0	3		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events will be recorded and reported at each study visit. Serious Adverse Event (SAE) forms. SAEs and SUSARs will be reported to the sponsor in accordance with the relevant local SOPs.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	3

Reporting groups

Reporting group title	Placebo
Reporting group description: -	
Reporting group title	Simvastatin

Reporting group description: -

Serious adverse events	Placebo	Simvastatin	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 16 (0.00%)	0 / 14 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	Placebo	Simvastatin	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	16 / 16 (100.00%)	14 / 14 (100.00%)	
General disorders and administration site conditions			
General disorder			
subjects affected / exposed	2 / 16 (12.50%)	1 / 14 (7.14%)	
occurrences (all)	2	1	
Gastrointestinal disorders			
Gastrointestinal disorder			
subjects affected / exposed	4 / 16 (25.00%)	1 / 14 (7.14%)	
occurrences (all)	4	1	
Respiratory, thoracic and mediastinal disorders			

Respiratory system disorder subjects affected / exposed occurrences (all)	4 / 16 (25.00%) 4	1 / 14 (7.14%) 2	
Skin and subcutaneous tissue disorders Dermatologic system disorders subjects affected / exposed occurrences (all)	4 / 16 (25.00%) 6	3 / 14 (21.43%) 3	
Psychiatric disorders Psychiatric disorders subjects affected / exposed occurrences (all)	5 / 16 (31.25%) 13	7 / 14 (50.00%) 7	
Musculoskeletal and connective tissue disorders Musculoskeletal system disorder subjects affected / exposed occurrences (all)	4 / 16 (25.00%) 4	2 / 14 (14.29%) 4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 October 2013	Protocol version 3.0 Endpoint outcome measures - added Effect on neurocognitive functions as assessed by the judgement of line orientation task and paired associate learning task. First trial visit (week 0) - added Cognitive functions will be assessed using the following neurocognitive measures: Judgement of line orientation task and paired associate learning task (20 minutes), removed genotyping, added Participants will be given stickers to positively reinforce the successful completion of the task. They will also be given a token of appreciation for their time and effort on the trial. Treatment procedures at 4 week visit - added genotyping, removed mononuclear PMAPKinase activity Trial treatment endpoint at 12 weeks - added Behavioural phenotype measures, Blood tests plasma lipids, liver function tests, renal function tests and creatine kinase, mononuclear PMAPkinase activity, Participants will be given a token of appreciation for their time and effort on the trial. Measuring trial endpoints - added Cognitive symptoms (baseline and 12 week end point) Assessed using the judgement of line orientation task, paired associate learning task. Data Collection - added Participants' cognitive functions will be assessed using the judgement of line orientation task and paired associate learning task and this will be recorded in the case record form.
30 May 2014	Protocol version 4.0 Amendment to patient recruitment age range, from 5-8 years to 4.5- 10.5 years. Cognitive assessment measures added at baseline and 12 weeks (Judgement of line orientation task & Paired associates learning task) Procedure for imaging - If it deemed appropriate, due to difficulties in week 0, the participant may require part of the scan or the entire scan to be performed at week 4. 4 week visit (+/- 7 days) - If required brain imaging will be undertaken on the MRI scanner at the CRF without contrast injections or sedation, with support from CRF staff, nursing and play specialists (e.g. if scan at week 0 was incomplete or inadequate)

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported