Clinical trial results:
A Phase II randomised placebo controlled clinical trial of Simvastatin in patients with secondary progressive multiple sclerosis

Summary

EudraCT number	2006-006347-31
Trial protocol	GB
Global end of trial date	14 November 2012

Results information

Result version number	v1 (current)
This version publication date	18 December 2019
First version publication date	18 December 2019

Trial information

Trial identification

Sponsor protocol code	MSTC-001 (MS-STAT)

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00647348
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Imperial College London
Sponsor organisation address	South Kensington Campus, London, United Kingdom, SW7 2AZ
Public contact	David Wilkie, Imperial College London, +44 02083830675, d.wilkie@imperial.ac.uk
Scientific contact	David Wilkie, Imperial College London, +44 02083830675, d.wilkie@imperial.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	01 November 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	14 November 2012
Global end of trial reached?	Yes
Global end of trial date	14 November 2012
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine whether Simvastatin at a dose of 80mg can reduce the rate of whole brain atrophy as measured by MRI over a 2-year time period when compared with placebo.

Protection of trial subjects:

None

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	28 January 2008
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: 140
Worldwide total number of subjects	140
EEA total number of subjects	140

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)	0
Adults (18-64 years)	140
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were recruited at three neuroscience centres in the UK between Jan 2008, and Nov 2011

Pre-assignment

Screening details:

140 participants enrolled to the study

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Simvastatin 80mg OD

Arm description:

Participants received Simvastatin 80mg OD

Arm type	Experimental
Investigational medicinal product name	Simvastatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

80mg daily, two 40 mg tablets inside opaque hard gelatine capsules
received one tablet per day for the first month before having two per day from then on for 24 months

Arm title	Placebo

Arm description:

Participants received Placebo

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

Dosage and administration details:

80mg daily, two 40 mg tablets inside opaque hard gelatine capsules
received one tablet per day for the first month before having two per day from then on for 24 months

Number of subjects in period 1	Simvastatin 80mg OD	Placebo
Started	70	70
Completed	67	64
Not completed	3	6
Lost to follow-up	3	6

Baseline characteristics

Reporting groups	
Reporting group title	Simvastatin 80mg OD
Reporting group description:	
Participants received Simvastatin 80mg OD	
Reporting group title	Placebo
Reporting group description:	
Participants received Placebo	

Reporting group values	Simvastatin 80mg OD	Placebo	Total
Number of subjects	70	70	140
Age categorical Units: Subjects			
Adults (18-64 years)	70	70	140
Age continuous Units: years			
geometric mean	51.5	51.1	
standard deviation	± 7	± 6.8	-
Gender categorical Units: Subjects			
Female	49	48	97
Male	21	22	43

End points

End points reporting groups

Reporting group title	Simvastatin 80mg OD
Reporting group description: Participants received Simvastatin 80mg OD	
Reporting group title	Placebo
Reporting group description: Participants received Placebo	

Primary: Percentage Change in Whole Brain Volume

End point title	Percentage Change in Whole Brain Volume
End point description:	
End point type	Primary
End point timeframe: 24 months	

End point values	Simvastatin 80mg OD	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	66	64		
Units: percentage of brain volumen change				
geometric mean (standard deviation)	0.288 (± 0.521)	0.584 (± 0.498)		

Statistical analyses

Statistical analysis title	Changes in Whole Brain Volume
Comparison groups	Simvastatin 80mg OD v Placebo
Number of subjects included in analysis	130
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	= 0.003
Method	BBSI=brain boundary shift integral

Notes:

[1] - intention-to-treat analysis

Secondary: Evaluation of Disability (EDSS)

End point title	Evaluation of Disability (EDSS)

End point description:

Score (0 to 10), lower score less disability and better progression. For EDSS, mean score at 24 months was compared between treatment groups using an ANCOVA model adjusting for baseline score and

minimisation variables.

End point type	Secondary

End point timeframe:

24 months

End point values	Simvastatin 80mg OD	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	67	61		
Units: score on scale				
geometric mean (standard deviation)	5.93 (± 1.11)	6.35 (± 0.83)		

Statistical analyses

Statistical analysis title	Evaluation of Disability (EDSS)
Comparison groups	Simvastatin 80mg OD v Placebo
Number of subjects included in analysis	128
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.05 [2]
Method	ANCOVA

Notes:

[2] - EDSS, mean score at 24 months was compared between treatment groups using an ANCOVA model adjusting for baseline score and minimisation variables.

Secondary: Evaluation of Disability (MSFC Z Score)

End point title	Evaluation of Disability (MSFC Z Score)

End point description:

Negative value implies worsening and a positive value implies improvement.

End point type	Secondary

End point timeframe:

24 months

End point values	Simvastatin 80mg OD	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	49		
Units: Score on scale				
geometric mean (standard deviation)	-0.78 (± 2.06)	-1.21 (± 2.59)		

Statistical analyses

No statistical analyses for this end point

Secondary: Evaluation of Disability (MSFC Walk)

End point title	Evaluation of Disability (MSFC Walk)

End point description:

The patient is directed to one end of a clearly marked 25-foot course and is instructed to walk 25 feet as quickly as possible, but safely. The time is calculated from the initiation of the instruction to start and ends when the patient has reached the 25-foot mark.

End point type	Secondary

End point timeframe:

24 months

End point values	Simvastatin 80mg OD	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	54		
Units: foot per second				
geometric mean (standard deviation)	1.83 (± 1.61)	1.55 (± 1.19)		

Statistical analyses

No statistical analyses for this end point

Secondary: Evaluation of Disability (MSFC Peg Test)

End point title	Evaluation of Disability (MSFC Peg Test)

End point description:

The patient is seated at a table with a small, shallow container holding nine pegs and a wood or plastic block containing nine empty holes. On a start command when a stopwatch is started, the patient picks up the nine pegs one at a time as quickly as possible, puts them in the nine holes, and, once they are in the holes, removes them again as quickly as possible one at a time, replacing them into the shallow container. The total time to complete the task is recorded.

End point type	Secondary

End point timeframe:

24 months

End point values	Simvastatin 80mg OD	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	54		
Units: speed per second				
geometric mean (standard deviation)	0.033 (± 0.01)	0.033 (± 0.01)		

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Impact Specific to the Disease and Rated by the Patient (MSIS-29 Questionnaire Total Score)

End point title	Disease Impact Specific to the Disease and Rated by the Patient (MSIS-29 Questionnaire Total Score)

End point description:

The MSIS-29 is a 29-item self-report measure with 20 items associated with a physical scale and 9 items with a psychological scale. Items ask about the impact of MS on day-to-day life in the past two weeks. All items have 5 response options: 1 "not at all" to 5"extremely". Each of the two scales is scored by summing the responses across items, then converting to a 0-100 scale where 100 indicates a greater impact of the disease on daily function (worse health).

End point type	Secondary

End point timeframe:

24 months

End point values	Simvastatin 80mg OD	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	66	57		
Units: score on a scale				
geometric mean (standard deviation)	70.1 (± 15.6)	76.1 (± 16.3)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 24 months	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	10
Reporting groups	
Reporting group title	Simvastatin 80mg OD
Reporting group description: Participants received Simvastatin 80mg OD	
Reporting group title	Placebo
Reporting group description: Participants received Placebo	

Serious adverse events	Simvastatin 80mg OD	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 70 (12.86%)	14 / 70 (20.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 70 (0.00%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fracture			
subjects affected / exposed	1 / 70 (1.43%)	2 / 70 (2.86%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			
subjects affected / exposed	0 / 70 (0.00%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Increased spasticity			

subjects affected / exposed	0 / 70 (0.00%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizures			
subjects affected / exposed	1 / 70 (1.43%)	0 / 70 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sub-arachnoid haemorrhage			
subjects affected / exposed	0 / 70 (0.00%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral encephalitis			
subjects affected / exposed	1 / 70 (1.43%)	0 / 70 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Grade 3 relapse (requiring hospital admission)			
subjects affected / exposed	3 / 70 (4.29%)	5 / 70 (7.14%)	
occurrences causally related to treatment / all	0 / 3	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal Lesion Biopsy			
subjects affected / exposed	0 / 70 (0.00%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendectomy			
subjects affected / exposed	0 / 70 (0.00%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pneumonia			

subjects affected / exposed	1 / 70 (1.43%)	0 / 70 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 70 (0.00%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	2 / 70 (2.86%)	0 / 70 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 70 (1.43%)	0 / 70 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Urinary tract infection			
subjects affected / exposed	2 / 70 (2.86%)	3 / 70 (4.29%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Simvastatin 80mg OD	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	49 / 70 (70.00%)	54 / 70 (77.14%)	
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 70 (4.29%)	10 / 70 (14.29%)	
occurrences (all)	3	10	
Relapse			
subjects affected / exposed	17 / 70 (24.29%)	17 / 70 (24.29%)	
occurrences (all)	17	17	
cramp			

subjects affected / exposed	12 / 70 (17.14%)	10 / 70 (14.29%)	
occurrences (all)	12	10	
Increase spasticity			
subjects affected / exposed	0 / 70 (0.00%)	7 / 70 (10.00%)	
occurrences (all)	0	7	
Worsening mobility			
subjects affected / exposed	9 / 70 (12.86%)	8 / 70 (11.43%)	
occurrences (all)	9	8	
General disorders and administration site conditions			
Pain			
subjects affected / exposed	7 / 70 (10.00%)	13 / 70 (18.57%)	
occurrences (all)	7	13	
Infections and infestations			
Urinary infection			
subjects affected / exposed	9 / 70 (12.86%)	8 / 70 (11.43%)	
occurrences (all)	9	8	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/24655729

http://www.ncbi.nlm.nih.gov/pubmed/28600189