Clinical trial results:
A phase 3 randomised, double blind, clinical trial investigating the effectiveness of repurposed simvastatin compared to placebo, in secondary progressive multiple sclerosis, in slowing the progression of disability

Summary

EudraCT number	2017-003328-56
Trial protocol	GB
Global end of trial date	26 July 2024

Results information

Result version number	v1 (current)
This version publication date	07 January 2026
First version publication date	07 January 2026

Trial information

Trial identification

Sponsor protocol code	CTU/2014/107

Additional study identifiers

ISRCTN number	ISRCTN82598726
ClinicalTrials.gov id (NCT number)	NCT03387670
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University College London
Sponsor organisation address	90 High Holborn, London, United Kingdom, WC1V 6LJ
Public contact	Chief Investigator, University College London, +44 2031087414, j.chataway@ucl.ac.uk
Scientific contact	Chief Investigator, University College London, +44 2031087414, j.chataway@ucl.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	11 October 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	26 July 2024
Global end of trial reached?	Yes
Global end of trial date	26 July 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to compare the effect of daily use simvastatin (80mg) versus placebo on disability progression at 6 monthly intervals in patients with Secondary Progressive MS (SPMS). Disability progression will be assessed based on change in Expanded Disability Status Scores (EDSS) compared to baseline.

The hypothesis is that repurposed simvastatin (80mg) is a disease modifying treatment for patients with SPMS.

Protection of trial subjects:

The trial was conducted in compliance with the approved protocol, UCL CCTU Standard Operating Procedures (SOPs), the Declaration of Helsinki (2008), the principles of Good Clinical Practice (GCP) as laid down by the Commission Directive 2005/28/EC with implementation in national legislation in the UK by Statutory Instrument 2004/1031 and subsequent amendments, the UK Data Protection Act, and the National Health Service (NHS) Research Governance Framework for Health and Social Care. The potential hepatic effects and risk of myopathy in simvastatin use and provision for stopping or modifiying treatment if these events occurred were made in the trial protocol.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 November 2017
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: 964
Worldwide total number of subjects	964
EEA total number of subjects	0

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	932
From 65 to 84 years	32
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were recruited from 31 neuroscience centres and district general hospitals in the UK.
The eligibility of each patient was reviewed on the observations and bloods taken for screening.

Pre-assignment

Screening details:

1079 participants were assessed for eligibility and 964 were randomised. The reasons for exclusions were: 94 ineligible, 16 patient choice and 5 unknown reason. Written informed consent to be was obtained, after explanation of the aims, methods, benefits and potential hazards of the trial and BEFORE any trial-specific procedures were performed.

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, Monitor, Assessor

Blinding implementation details:

Participants and investigators, including pharmacy, treating and independent assessing neurologists, were masked to treatment allocation. To maintain masking, an online randomisation system was used. This issued a five-digit code to identify the concealed bottles of treatment (tablets of the same colour and size), either simvastatin or placebo, for the site pharmacy to dispense at each dosing visit according to the patient's allocation.

Arms

Are arms mutually exclusive?	Yes
Arm title	Simvastatin

Arm description:

Oral 80mg simvastatin (initially 40mg at randomisation, then escalated after 1 month if tolerated) taken once daily at night

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

Dosage and administration details:

Oral 80mg simvastatin (initially 40mg at randomisation, then escalated after 1 month if tolerated) taken once daily at night.

Arm title	Placebo

Arm description:

Oral placebo (initially 1 capsule at randomisation, then escalated after 1 month to 2 capsules if tolerated), taken once daily at night.

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

Dosage and administration details:

Placebo (1x tablet taken once daily at night for 1 month from Baseline (Month 0). Followed by Placebo (2x tablet taken once daily at night) for 35 months from Visit 3 (Month 1) to Visit 10 (Month 36). For

those patients who have not had a confirmed EDSS progression event by Visit 10 (Month 36), they will be invited to an additional 3 visits to Visit 13 (Month 54) to continue Placebo (2x tablet taken once daily at night).

Number of subjects in period 1	Simvastatin	Placebo
Started	482	482
Completed	425	412
Not completed	57	70
Consent withdrawn by subject	28	32
Unable to complete safety monitoring	1	6
Adverse event, non-fatal	14	14
Started contraindicated medication	-	1
Ill health	6	9
Safety concerns	3	1
Started statins	-	3
Died	5	4

Baseline characteristics

Reporting groups	
Reporting group title	Simvastatin
Reporting group description:	
Oral 80mg simvastatin (initially 40mg at randomisation, then escalated after 1 month if tolerated) taken once daily at night	
Reporting group title	Placebo
Reporting group description:	
Oral placebo (initially 1 capsule at randomisation, then escalated after 1 month to 2 capsules if tolerated), taken once daily at night.	

Reporting group values	Simvastatin	Placebo	Total
Number of subjects	482	482	964
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			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)			0
From 65-84 years			0
85 years and over			0
Age continuous			
Age at randomisation			
Units: years			
arithmetic mean	54.2	54.4	
standard deviation	± 6.8	± 6.8	-
Gender categorical Units: Subjects			
Female	353	351	704
Male	129	131	260
Ethnic origin Units: Subjects			
White	463	466	929
Asian or Asian British	12	9	21
Black or Black British	1	3	4
Mixed	6	3	9
Unknown	0	1	1
Relapse in last 12 months			
Has the participant had a relapse in the last 12 months before randomisation			
Units: Subjects			
Yes	25	24	49
No	457	458	915
Expanded Disability Status Scale step score			

Expanded Disability Status Scale step score at randomistion			
Units: Subjects			
4 to 5.5	140	135	275
6.0	177	177	354
6.5	165	170	335
Symbol Digit Modalities Test Z score ≤−1·5			
Number and % of participants with Z score of under ≤−1·5 on the Symbol Digit Modalities Test.			
Units: Subjects			
≤−1·5	270	253	523
>-1.5	204	217	421
Missing	8	12	20
California Verbal Learning Test-II Z score ≤−1.5 Units: Subjects			
≤−1.5	171	176	347
>-1.5	302	294	596
Missing	9	12	21
Brief Visuospatial Memory Test-Revised Z score ≤−1.5 Units: Subjects			
≤−1.5	55	57	112
>-1.5	415	401	816
Missing	12	24	36
Siponimod			
On siponimod treatment at randomisation			
Units: Subjects			
Yes	1	0	1
No	481	482	963
Multiple Sclerosis Duration			
Years since onset of multiple sclerosis			
Units: Years			
arithmetic mean	22.3	23.4	
standard deviation	± 9.4	± 9.4	-
Secondary progressive multiple sclerosis duration			
Years since onset of secondary progressive multiple sclerosis			
Units: Years			
arithmetic mean	7.0	7.2	
standard deviation	± 4.7	± 5.0	-
Total cholesterol Units: mmol/L			
arithmetic mean	5.4	5.4	
standard deviation	± 1.1	± 1.1	-
Timed 25-foot walk speed			
Speed at completing the 2 trials of the MSFC timed 25 foot walk at the baseline visit			
Units: feet per second			
arithmetic mean	2.2	2.2	
standard deviation	± 1.2	± 1.2	-
9 hole peg test speed			
Speed at completing the MSFC nine hole peg test			
Units: s-1 x 100			
arithmetic mean	3.3	3.4	

standard deviation	± 1.0	± 1.0	-
Multiple sclerosis impact scale physical score			
Multiple sclerosis impact scale physical score out of 100			
Units: Score from 0 to 100			
arithmetic mean	54.3	54.6	
standard deviation	± 19.4	± 19.2	-
Multiple sclerosis impact scale psychological score			
Multiple sclerosis impact scale psychological score out of 100			
Units: Score from 0 to 100			
arithmetic mean	38.4	40.2	
standard deviation	± 21.6	± 22.5	-
Multiple Sclerosis Walking Scale-12 version 2			
Multiple Sclerosis Walking Scale-12 version 2 score out of 100			
Units: Score from 0 to 100			
arithmetic mean	67.9	66.7	
standard deviation	± 18.0	± 18.4	-
Modified Fatigue Impact Scale 21			
Modified Fatigue Impact Scale 21 score out of 100			
Units: Score from 0 to 100			
arithmetic mean	57.5	57.0	
standard deviation	± 19.2	± 19.5	-
Chalder Fatigue Questionnaire			
Chalder Fatigue Questionnaire score out of 100			
Units: Score from 0 to 100			
arithmetic mean	52.8	52.3	
standard deviation	± 18.6	± 19.0	-
Sloan low contrast visual acuity 100% contrast			
Number of letters identified on Sloan chart at 100% contrast, out of 60			
Units: Letters			
arithmetic mean	51.3	51.1	
standard deviation	± 10.1	± 10.4	-
Sloan low contrast visual acuity 2.5% contrast			
Number of letters correctly identified on Sloan low contrast visual acuity 2.5% contrast			
Units: Letters			
arithmetic mean	26.3	25.9	
standard deviation	± 13.0	± 13.2	-
Sloan low contrast visual acuity 1.25% contrast			
Number of letters correctly identified on Sloan low contrast visual acuity at 1.25% contrast			
Units: Letters			
arithmetic mean	13.7	13.7	
standard deviation	± 12.1	± 12.2	-

End points

End points reporting groups

Reporting group title	Simvastatin

Reporting group description:

Oral 80mg simvastatin (initially 40mg at randomisation, then escalated after 1 month if tolerated) taken once daily at night

Reporting group title	Placebo

Reporting group description:

Oral placebo (initially 1 capsule at randomisation, then escalated after 1 month to 2 capsules if tolerated), taken once daily at night.

Subject analysis set title	Per-protocol high dose
Subject analysis set type	Per protocol

Subject analysis set description:

Includes participants who complied with high dose treatment. Patients were considered compliant with their randomised intervention if they took the protocol dose on at least 90% of days over the first 3 years of follow-up, or until date of confirmed progression, death, or withdrawal if these happened before 3 years.

Subject analysis set title	Per-protocol high/low dose
Subject analysis set type	Per protocol

Subject analysis set description:

Includes participants who complied with high or low dose treatment. Patients were considered compliant with their randomised intervention if they took the either low (40mg/1 capsule) or high (80mg/2 capsules) dose on at least 90% of days over the first 3 years of follow-up, or until date of confirmed progression, death, or withdrawal if these happened before 3 years.

Subject analysis set title	COVID-19 sensitivity analysis
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants were included where they were randomised before the start of COVID-19-related public health restrictions (before March 16, 2020) and attended an in-person visit at month 36 after the end of COVID-19 related public health restrictions in the UK (after July 19, 2021).

Primary: Confirmed disability progression up to 4·5 years

End point title	Confirmed disability progression up to 4·5 years

End point description:

The primary endpoint was confirmed disability progression up to 4·5 years. Progression of disability was defined as an increase of at least 1 point if EDSS score at baseline visit was less than 6·0, or an increase of 0·5 point if EDSS score at baseline visit was 6·0 or more. The initial disability progression event was finalised as a confirmed event if the increase in EDSS persisted to at the next visit at least 6 months later. The time of confirmed progression was defined as when the initial disability progression occurred.

End point type	Primary

End point timeframe:

Up to 4.5 years from randomisation

End point values	Simvastatin	Placebo	Per-protocol high dose	Per-protocol high/low dose
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	482	482	646	681
Units: Progression				
Yes	192	173	264	274
No	290	309	382	407

End point values	COVID-19 sensitivity analysis			
Subject group type	Subject analysis set			
Number of subjects analysed	615			
Units: Progression				
Yes	203			
No	412			

Statistical analyses

Statistical analysis title	Primary endpoint: confirmed disability progression

Statistical analysis description:

The primary endpoint, confirmed disability progression on EDSS, was compared between the simvastatin and placebo treatment using a Cox proportional hazards model. The estimated hazard ratio (HR) along with its 95% confidence interval (CI) and Wald test p value was obtained. The model stratified by centre and adjusted for the other variables included in the minimisation process (sex, age, and baseline EDSS).

Comparison groups	Simvastatin v Placebo
Number of subjects included in analysis	964
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.26 [1]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.91
upper limit	1.39

Notes:

[1] - Two-sided p-value from a Wald test against the null hypothesis that the hazard ratio is equal to 1

Statistical analysis title	Sensitivity analysis including unconfirmed events

Statistical analysis description:

Simvastatin and placebo groups were compared using a Cox proportional hazards model that stratified by centre and adjusted for the other variables included in the minimisation process (sex, age, and baseline EDSS). In this analysis progression events were additionally included where participant ended follow-up before the event could be confirmed.

Comparison groups	Simvastatin v Placebo
Number of subjects included in analysis	964
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	= 0.32 [3]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.1

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.91
upper limit	1.33

Notes:

[2] - Sensitivity analysis for the primary endpoint

[3] - Two-sided p-value from a Wald test against the null hypothesis that the hazard ratio is equal to 1

Statistical analysis title	Per-protocol analysis, high dose

Statistical analysis description:

The primary endpoint, confirmed disability progression on EDSS, was compared between the simvastatin and placebo treatment using a Cox proportional hazards model. The estimated hazard ratio (HR) along with its 95% confidence interval (CI) and Wald test p value was obtained. The model stratified by centre and adjusted for the other variables included in the minimisation process (sex, age, and baseline EDSS).

Comparison groups	Simvastatin v Placebo v Per-protocol high dose
Number of subjects included in analysis	1610
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	= 0.38
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.87
upper limit	1.43

Notes:

[4] - Per-protocol analysis including participants who complied with high dose treatment

Statistical analysis title	Per-protocol analysis, low/high dose

Statistical analysis description:

The primary endpoint, confirmed disability progression on EDSS, was compared between the simvastatin and placebo treatment using a Cox proportional hazards model. The estimated hazard ratio (HR) along with its 95% confidence interval (CI) and Wald test p value was obtained. The model stratified by centre and adjusted for the other variables included in the minimisation process (sex, age, and baseline EDSS).

Comparison groups	Simvastatin v Placebo v Per-protocol high/low dose
Number of subjects included in analysis	1645
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	= 0.37
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.88
upper limit	1.42

Notes:

[5] - Per-protocol analysis including participants who complied with high or low dose treatment

Statistical analysis title	Covid-19 sensitivity analysis

Statistical analysis description:

A mixed-effects logistic regression model was used to compare the placebo and simvastatin group at 3 years on unconfirmed progression on the EDSS step score. Analysis adjusted for sex, age, and baseline EDSS and included a random effect for site.

Comparison groups	Simvastatin v Placebo v COVID-19 sensitivity analysis
Number of subjects included in analysis	1579
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.85
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.73
upper limit	1.45

Secondary: Multicomponent disability progression

End point title	Multicomponent disability progression

End point description:

Progression by 3 years on a multicomponent measure. Disability progression (and subsequently confirmed) on one or more of EDSS, timed 25-foot walk (T25FW), or the 9 hole peg test (9HPT). Progression on the EDSS was defined as a 0·5 point increase if baseline EDSS ≥6 or 1·0 point increase if baseline EDSS <6. Progression on the MSFC walk was defined as either: A) ≥20% increase in average 25ft walk time; or B) becoming unable to complete either of the trials of the 25ft walk due to disability. Progression on the 9HPTwas defined as either: A) ≥20% decrease in the average 9HPT time; B) becoming unable to complete either of the right handed trials of the 9HPT; or C) becoming unable to complete either of the left handed trials of the 9HPT.

End point type	Secondary

End point timeframe:

Up to 3 years.

End point values	Simvastatin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	446[6]	442[7]		
Units: Progression				
Yes	261	242		
No	185	200		

Notes:

[6] - Participants were only included where they had a valid measure of the outcome

[7] - Participants only included where they had a valid measure of the outcome

Statistical analyses

Statistical analysis title	Mixed effects logistic regression

Statistical analysis description:

A mixed-effects logistic regression model was used to compare the groups at 3 years on subsequently confirmed disability progression on the multicomponent measure. Analysis adjusted for sex, age, and baseline EDSS and included a random effect for site.

Comparison groups	Simvastatin v Placebo
Number of subjects included in analysis	888
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.26
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.89
upper limit	1.53

Secondary: Multicomponent disability progression: EDSS

End point title	Multicomponent disability progression: EDSS

End point description:

Progression by 3 years on EDSS (and subsequently confirmed) for participants with data on multicomponent measure of disability progression. Progression on the EDSS was defined as per the primary outcome: a 0·5 point increase if baseline EDSS ≥6 or 1·0 point increase if baseline EDSS <6.

End point type	Secondary

End point timeframe:

Up to 3 years from randomisation

End point values	Simvastatin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	446	442		
Units: Progression				
Yes	166	150		
No	276	292		

Statistical analyses

Statistical analysis title	Mixed effects logistic regression

Statistical analysis description:

A mixed-effects logistic regression model was used to compare the groups at 3 years on subsequently confirmed disability progression on the multicomponent measure. Analysis adjusted for sex, age, and baseline EDSS and included a random effect for site.

Comparison groups	Simvastatin v Placebo

Number of subjects included in analysis	888
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.34
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.87
upper limit	1.52

Secondary: Multicomponent disability progression: Timed 25-foot walk

End point title	Multicomponent disability progression: Timed 25-foot walk

End point description:

Progression by 3 years on timed 25-foot walk (and subsequently confirmed). Analysis includes participants with data on the multicomponent measure of disability progression. Progression on the MSFC walk was defined as either: A) ≥20% increase in average 25ft walk time; or B) becoming unable to complete either of the trials of the 25ft walk due to disability.

End point type	Secondary

End point timeframe:

Up to 3 years

End point values	Simvastatin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	446	442		
Units: Progression				
Yes	158	145		
No	288	297		

Statistical analyses

Statistical analysis title	Mixed effects logistic regression

Statistical analysis description:

A mixed-effects logistic regression model was used to compare the groups at 3 years on confirmed disability progression. Analysis adjusted for sex, age, and baseline EDSS and included a random effect for site.

Comparison groups	Simvastatin v Placebo

Number of subjects included in analysis	888
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.39
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.85
upper limit	1.52

Secondary: Multicomponent disability progression: 9 hole peg test

End point title	Multicomponent disability progression: 9 hole peg test

End point description:

Progression by 3 years (and subsequently confirmed) on the 9 hole peg test (9HPT). Progression on the 9HPTwas defined as either: A) ≥20% decrease in the average 9HPT time; B) becoming unable to complete either of the right handed trials of the 9HPT; or C) becoming unable to complete either of the left handed trials of the 9HPT.

End point type	Secondary

End point timeframe:

Up to 3 years

End point values	Simvastatin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	446	442		
Units: Progression				
Yes	51	32		
No	395	410		

Statistical analyses

Statistical analysis title	Mixed effects logistic regression

Statistical analysis description:

A mixed-effects logistic regression model was used to compare the groups at 3 years. Analysis adjusted for sex, age, and baseline EDSS and included a random effect for site.

Comparison groups	Simvastatin v Placebo
Number of subjects included in analysis	888
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.031
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.68

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.05
upper limit	2.69

Secondary: Modified Rankin Scale

End point title	Modified Rankin Scale

End point description:

Disability progression on the mRS, defined as any increase between baseline and 3 years.

End point type	Secondary

End point timeframe:

At 3 years

End point values	Simvastatin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	413	393		
Units: Progression				
Yes	165	148		
No	248	245		

Statistical analyses

Statistical analysis title	Mixed effects logistic regression

Statistical analysis description:

A mixed-effects logistic regression model was used to compare the groups at 3 years. Analysis adjusted for sex, age, and baseline EDSS and included a random effect for site.

Comparison groups	Simvastatin v Placebo
Number of subjects included in analysis	806
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.53
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.82
upper limit	1.47

Secondary: Multiple Sclerosis Functional Composite Z score

End point title	Multiple Sclerosis Functional Composite Z score

End point description:

Multiple Sclerosis Functional Composite (MSFC) Z score comprising the timed 25-foot walk, 9 hole peg test and Symbol Digit Modalities Test. Z score is standardised using the baseline of the MS-STAT2 study.

End point type	Secondary

End point timeframe:

At 3 years

End point values	Simvastatin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	402	383		
Units: Z score				
arithmetic mean (standard deviation)	-0.3 (± 1.2)	-0.3 (± 1.2)		

Statistical analyses

Statistical analysis title	Mixed effects linear regression

Statistical analysis description:

The groups were compared using a mixed effects linear regression for the outcome at baseline and 3 years, with the treatment effect at baseline constrained to zero. The model included an unstructured covariance matrix for the residuals. The minimisation variables (i.e., sex, age, and baseline EDSS) and their interactions with visit were included as fixed effects. Bias corrected and accelerated bootstrap 95% CI based on 2000 replications were used for inference.

Comparison groups	Simvastatin v Placebo
Number of subjects included in analysis	785
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05 [8]
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.09
upper limit	0.14

Notes:

[8] - P-value inferred from 95% confidence intervals.

Secondary: Timed 25ft walk speed

End point title	Timed 25ft walk speed

End point description:

Analysis of the 25ft walk used the reciprocal of the average 25ft walk time. Where a trial could not be completed due to disability the maximum possible time of 180 seconds was imputed

End point type	Secondary

End point timeframe:

At 3 years

End point values	Simvastatin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	389	373		
Units: Feet per second				
arithmetic mean (standard deviation)	1.9 (± 1.2)	1.9 (± 1.3)		

Statistical analyses

Statistical analysis title	Mixed effects linear regression

Statistical analysis description:

The groups were compared using a mixed effects linear regression for the outcome at baseline and 3 years, with the treatment effect at baseline constrained to zero. The model included an unstructured covariance matrix for the residuals. The minimisation variables (i.e., sex, age, and baseline EDSS) and their interactions with visit were included as fixed effects.

Comparison groups	Simvastatin v Placebo
Number of subjects included in analysis	762
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.88
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	-0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.12
upper limit	0.1

Secondary: 9-hole peg test speed

End point title	9-hole peg test speed

End point description:

Speed at completing the 9 hole peg test. Analysis of the 9HPT used was based on average 1/9HPT as defined in the MSFC manual. Where participants could not complete a trial due to disability the maximum possible time was imputed which was 300 seconds.

End point type	Secondary

End point timeframe:

At 3 years

End point values	Simvastatin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	401	383		
Units: seconds^-1 x 100				
arithmetic mean (standard deviation)	3.3 (± 1.1)	3.3 (± 1.1)		

Statistical analyses

Statistical analysis title	Mixed effects linear regression

Statistical analysis description:

The groups were compared using a mixed effects linear regression for the outcome at baseline and 3 years, with the treatment effect at baseline constrained to zero. The model included an unstructured covariance matrix for the residuals. The minimisation variables (i.e., sex, age, and baseline EDSS) and their interactions with visit were included as fixed effects.

Comparison groups	Simvastatin v Placebo
Number of subjects included in analysis	784
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.48
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.05
upper limit	0.12

Secondary: Symbol Digit Modalities Test score

End point title	Symbol Digit Modalities Test score

End point description:

Symbol Digit Modalities Test score out of 110

End point type	Secondary

End point timeframe:

At 3 years

End point values	Simvastatin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	397	377		
Units: Score from 0 to 110				
arithmetic mean (standard deviation)	43.3 (± 13.9)	43.8 (± 13.7)		

Statistical analyses

Statistical analysis title	Mixed effects linear regression

Statistical analysis description:

The groups were compared using a mixed effects linear regression for the outcome at baseline and 3 years, with the treatment effect at baseline constrained to zero. The model included an unstructured covariance matrix for the residuals. The minimisation variables (i.e., sex, age, and baseline EDSS) and their interactions with visit were included as fixed effects.

Comparison groups	Simvastatin v Placebo
Number of subjects included in analysis	774
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.87
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.25
upper limit	1.06

Secondary: Sloan Low Contrast Visual Acuity 100% contrast

End point title	Sloan Low Contrast Visual Acuity 100% contrast

End point description:

Number of letters correctly identified out of 60

End point type	Secondary

End point timeframe:

3 years

End point values	Simvastatin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	389	369		
Units: Letters				
arithmetic mean (standard deviation)	50.5 (± 9.5)	50.0 (± 10.7)		

Statistical analyses

Statistical analysis title	Mixed effects linear regression

Statistical analysis description:

The groups were compared using a mixed effects linear regression for the outcome at baseline and 3 years, with the treatment effect at baseline constrained to zero. The model included an unstructured covariance matrix for the residuals. The minimisation variables (i.e., sex, age, and baseline EDSS) and their interactions with visit were included as fixed effects. Bias corrected and accelerated bootstrap 95% CI based on 2000 replications were used for inference.

Comparison groups	Simvastatin v Placebo
Number of subjects included in analysis	758
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05 [9]
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.01
upper limit	1.16

Notes:

[9] - P value inferred from 95% confidence intervals

Secondary: Sloan Low Contrast Visual Acuity 2.5% contrast

End point title	Sloan Low Contrast Visual Acuity 2.5% contrast

End point description:

Number of letters correctly identified out of 60

End point type	Secondary

End point timeframe:

At 3 years

End point values	Simvastatin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	388	366		
Units: Letters				
arithmetic mean (standard deviation)	25.6 (± 12.6)	24.5 (± 12.2)		

Statistical analyses

Statistical analysis title	Mixed effects linear regression

Statistical analysis description:

The groups were compared using a mixed effects linear regression for the outcome at baseline and 3 years, with the treatment effect at baseline constrained to zero. The model included an unstructured covariance matrix for the residuals. The minimisation variables (i.e., sex, age, and baseline EDSS) and their interactions with visit were included as fixed effects. Bias corrected and accelerated bootstrap 95% CI based on 2000 replications were used for inference.

Comparison groups	Simvastatin v Placebo

Number of subjects included in analysis	754
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05 [10]
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.79
upper limit	1.81

Notes:

[10] - P-value inferred from 95% confidence interval

Secondary: Sloan Low Contrast Visual Acuity 1.25% contrast

End point title	Sloan Low Contrast Visual Acuity 1.25% contrast

End point description:

Number of letters correctly identified out of 60

End point type	Secondary

End point timeframe:

At 3 years

End point values	Simvastatin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	376	362		
Units: Letters				
arithmetic mean (standard deviation)	12.7 (± 11.8)	12.8 (± 11.1)		

Statistical analyses

Statistical analysis title	Mixed effects linear regression

Statistical analysis description:

The groups were compared using a mixed effects linear regression for the outcome at baseline and 3 years, with the treatment effect at baseline constrained to zero. The model included an unstructured covariance matrix for the residuals. The minimisation variables (i.e., sex, age, and baseline EDSS) and their interactions with visit were included as fixed effects. Bias corrected and accelerated bootstrap 95% CI based on 2000 replications were used for inference.

Comparison groups	Simvastatin v Placebo
Number of subjects included in analysis	738
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05 [11]
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	-0.49

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.8
upper limit	0.76

Notes:

[11] - P-value inferred from 95% confidence interval

Secondary: California Verbal Learning Test-II

End point title	California Verbal Learning Test-II

End point description:

California Verbal Learning Test-II score out of 80

End point type	Secondary

End point timeframe:

At 3 years

End point values	Simvastatin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	399	378		
Units: Score from 0 to 80				
arithmetic mean (standard deviation)	46.8 (± 13.0)	47.0 (± 13.3)		

Statistical analyses

Statistical analysis title	Mixed effects linear regression

Statistical analysis description:

The groups were compared using a mixed effects linear regression for the outcome at baseline and 3 years, with the treatment effect at baseline constrained to zero. The model included an unstructured covariance matrix for the residuals. The minimisation variables (i.e., sex, age, and baseline EDSS) and their interactions with visit were included as fixed effects.

Comparison groups	Simvastatin v Placebo
Number of subjects included in analysis	777
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.95
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	-0.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.32
upper limit	1.24

Secondary: Brief Visuospatial Memory Test-Revised

End point title	Brief Visuospatial Memory Test-Revised
End point description:	
Brief Visuospatial Memory Test-Revised score out of 36	
End point type	Secondary
End point timeframe:	
At 3 years	

End point values	Simvastatin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	386	366		
Units: Score from 0 to 36				
arithmetic mean (standard deviation)	20.2 (± 8.7)	20.3 (± 9.3)		

Statistical analyses

Statistical analysis title	Mixed effects linear regression
Statistical analysis description:	
The groups were compared using a mixed effects linear regression for the outcome at baseline and 3 years, with the treatment effect at baseline constrained to zero. The model included an unstructured covariance matrix for the residuals. The minimisation variables (i.e., sex, age, and baseline EDSS) and their interactions with visit were included as fixed effects.	
Comparison groups	Simvastatin v Placebo
Number of subjects included in analysis	752
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.57
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.67
upper limit	1.22

Secondary: Multiple sclerosis impact scale 29 version 2 Total

End point title	Multiple sclerosis impact scale 29 version 2 Total
End point description:	
Total score out of 100 on the Multiple sclerosis impact scale 29 version 2	
End point type	Secondary
End point timeframe:	
At 3 years	

End point values	Simvastatin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	397	387		
Units: Score from 0 to 100				
arithmetic mean (standard deviation)	51.1 (± 19.7)	50.5 (± 20.4)		

Statistical analyses

Statistical analysis title	Mixed effects linear regression

Statistical analysis description:

The mean at 3 years was compared between the groups using mixed effects linear regression for the outcome at baseline, 1, 2 and 3 years. The model included an interaction between visit and treatment group, with the treatment effects at baseline constrained to be zero. The minimisation variables (sex, age, and baseline EDSS) and their interactions with visit were included as fixed effects. The model included an unstructured covariance matrix for the residuals by visit.

Comparison groups	Simvastatin v Placebo
Number of subjects included in analysis	784
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.15
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	1.57
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.55
upper limit	3.68

Secondary: Multiple sclerosis impact scale 29 version 2 physical score

End point title	Multiple sclerosis impact scale 29 version 2 physical score

End point description:

Multiple sclerosis impact scale 29 version 2 physical score out of 100

End point type	Secondary

End point timeframe:

At 3 years

End point values	Simvastatin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	401	389		
Units: Score from 0 to 100				
arithmetic mean (standard deviation)	56.8 (± 21.2)	55.3 (± 21.3)		

Statistical analyses

Statistical analysis title	Mixed effects linear regression

Statistical analysis description:

The mean at 3 years was compared between the groups using mixed effects linear regression for the outcome at baseline, 1, 2 and 3 years. The model included an interaction between visit and treatment group, with the treatment effects at baseline constrained to be zero. The minimisation variables (sex, age, and baseline EDSS) and their interactions with visit were included as fixed effects. The model included an unstructured covariance matrix for the residuals by visit.

Comparison groups	Simvastatin v Placebo
Number of subjects included in analysis	790
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.09
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	1.97
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.28
upper limit	4.22

Secondary: Multiple sclerosis impact scale 29 version 2 psychological score

End point title	Multiple sclerosis impact scale 29 version 2 psychological score

End point description:

Multiple sclerosis impact scale 29 version 2 (out of 100)

End point type	Secondary

End point timeframe:

At 3 years

End point values	Simvastatin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	411	405		
Units: Score from 0 to 100				
arithmetic mean (standard deviation)	39.1 (± 22.8)	39.8 (± 23.8)		

Statistical analyses

Statistical analysis title	Mixed effects linear regression

Statistical analysis description:

The mean at 3 years was compared between the groups using mixed effects linear regression for the outcome at baseline, 1, 2 and 3 years. The model included an interaction between visit and treatment group, with the treatment effects at baseline constrained to be zero. The minimisation variables (sex, age, and baseline EDSS) and their interactions with visit were included as fixed effects. The model included an unstructured covariance matrix for the residuals by visit.

Comparison groups	Placebo v Simvastatin
Number of subjects included in analysis	816
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.48
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.57
upper limit	3.32

Secondary: Multiple Sclerosis Walking Scale 12

End point title	Multiple Sclerosis Walking Scale 12

End point description:

Multiple Sclerosis Walking Scale 12 score out of 100

End point type	Secondary

End point timeframe:

At 3 years

End point values	Simvastatin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	394	386		
Units: Score from 0 to 100				
arithmetic mean (standard deviation)	68.3 (± 21.0)	69.0 (± 20.9)		

Statistical analyses

Statistical analysis title	Mixed effects linear regression

Statistical analysis description:

The mixed effects linear regression for the outcome at baseline, 1, 2 and 3 years included fixed effects for the interactions between visit and treatment group, minimisation variables and their interactions with visit. The treatment effect at baseline was constrained to zero. There was an unstructured covariance matrix for the residuals. Bias corrected and accelerated bootstrap 95% CI based on 2000 replications were used for inference.

Comparison groups	Simvastatin v Placebo
Number of subjects included in analysis	780
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05 [12]
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	-1.38
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.61
upper limit	0.74

Notes:

[12] - P value inferred from 95% confidence intervals

Secondary: Modified Fatigue Impact Scale 21

End point title	Modified Fatigue Impact Scale 21

End point description:

Modified Fatigue Impact Scale 21 score out of 100

End point type	Secondary

End point timeframe:

At 3 years

End point values	Simvastatin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	391	377		
Units: Score from 0 to 100				
arithmetic mean (standard deviation)	56.2 (± 20.9)	54.7 (± 21.7)		

Statistical analyses

Statistical analysis title	Mixed effects linear regression

Statistical analysis description:

The mean at 3 years was compared between the groups using mixed effects linear regression for the outcome at baseline, 1, 2 and 3 years. The model included an interaction between visit and treatment group, with the treatment effects at baseline constrained to be zero. The minimisation variables (sex, age, and baseline EDSS) and their interactions with visit were included as fixed effects. The model included an unstructured covariance matrix for the residuals by visit.

Comparison groups	Simvastatin v Placebo
Number of subjects included in analysis	768
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.41
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.31
upper limit	3.23

Secondary: Chalder Fatigue Questionnaire

End point title	Chalder Fatigue Questionnaire
End point description:	
Chalder Fatigue Questionnaire score out of 100	
End point type	Secondary
End point timeframe:	
At 3 years	

End point values	Simvastatin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	403	398		
Units: Score from 0 to 100				
arithmetic mean (standard deviation)	50.4 (± 18.2)	49.0 (± 18.1)		

Statistical analyses

Statistical analysis title	Mixed effects linear regression

Statistical analysis description:

The mean at 3 years was compared between the groups using mixed effects linear regression for the outcome at baseline, 1, 2 and 3 years. The model included an interaction between visit and treatment group, with the treatment effects at baseline constrained to be zero. The minimisation variables (sex, age, and baseline EDSS) and their interactions with visit were included as fixed effects. The model included an unstructured covariance matrix for the residuals by visit.

Comparison groups	Simvastatin v Placebo
Number of subjects included in analysis	801
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.29
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	1.22

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.04
upper limit	3.48

Secondary: Relapses

End point title	Relapses
End point description:	
Number of relapses	
End point type	Secondary
End point timeframe:	
Up to 3 years	

End point values	Simvastatin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	482	482		
Units: Number	98	68		

Statistical analyses

Statistical analysis title	Negative binomial regression
Statistical analysis description:	
Relapse rate was compared between the simvastatin and placebo groups using a mixed-effects negative binomial regression model with follow-up time for each participant included as an offset in the model. Analysis adjusted for sex, age, and baseline EDSS and included a random effect for site.	
Comparison groups	Simvastatin v Placebo
Number of subjects included in analysis	964
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.044
Method	Negative binomial regression
Parameter estimate	Incidence rate ratio
Point estimate	1.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.01
upper limit	2.01

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From randomisation up to the end of each participant's follow-up, which was up to 4.5 years.	
Adverse event reporting additional description:	
Non-serious adverse events are reported by system organ class.	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	26

Reporting groups	
Reporting group title	Simvastatin
Reporting group description:	
Oral 80mg simvastatin (initially 40mg at randomisation, then escalated after 1 month if tolerated) taken once daily at night	
Reporting group title	Placebo
Reporting group description:	
Oral placebo (initially 1 capsule at randomisation, then escalated after 1 month to 2 capsules if tolerated), taken once daily at night.	

Serious adverse events	Simvastatin	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	124 / 482 (25.73%)	117 / 482 (24.27%)	
number of deaths (all causes)	5	4	
number of deaths resulting from adverse events	5	4	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	3 / 482 (0.62%)	6 / 482 (1.24%)	
occurrences causally related to treatment / all	0 / 3	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder cancer			
subjects affected / exposed	0 / 482 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cholangiocarcinoma			
subjects affected / exposed	0 / 482 (0.00%)	2 / 482 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Lung cancer			
subjects affected / exposed	1 / 482 (0.21%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melanoma			
subjects affected / exposed	0 / 482 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningioma			
subjects affected / exposed	0 / 482 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuroendocrine Tumour			
subjects affected / exposed	1 / 482 (0.21%)	0 / 482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oropharyngeal cancer			
subjects affected / exposed	1 / 482 (0.21%)	0 / 482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Ovarian cancer			
subjects affected / exposed	2 / 482 (0.41%)	0 / 482 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Prostate cancer			
subjects affected / exposed	0 / 482 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal tumour			
subjects affected / exposed	1 / 482 (0.21%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Squamous cell carcinoma			

subjects affected / exposed	4 / 482 (0.83%)	0 / 482 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
deep vein thrombosis			
subjects affected / exposed	0 / 482 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	0 / 482 (0.00%)	2 / 482 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	2 / 482 (0.41%)	2 / 482 (0.41%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Right superior femoral artery thrombosis			
subjects affected / exposed	0 / 482 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Cholecystectomy			
subjects affected / exposed	1 / 482 (0.21%)	0 / 482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip replacement revision			
subjects affected / exposed	0 / 482 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hysterectomy			
subjects affected / exposed	0 / 482 (0.00%)	2 / 482 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Insertion of suprapubic catheter			
subjects affected / exposed	0 / 482 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
MS Autologous Stem Cell Transplant			
subjects affected / exposed	0 / 482 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Right foot bones fusion surgery			
subjects affected / exposed	1 / 482 (0.21%)	0 / 482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stoma creation			
subjects affected / exposed	1 / 482 (0.21%)	0 / 482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Finger surgery			
subjects affected / exposed	1 / 482 (0.21%)	0 / 482 (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			
Reaction to COVID vaccine			
subjects affected / exposed	1 / 482 (0.21%)	0 / 482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
hysteroscopy and polypectomy			
subjects affected / exposed	1 / 482 (0.21%)	0 / 482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine bleeding			
subjects affected / exposed	1 / 482 (0.21%)	0 / 482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Respiratory, thoracic and mediastinal disorders			
Asthma exacerbation			
subjects affected / exposed	1 / 482 (0.21%)	0 / 482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia, parapneumonic effusion			
subjects affected / exposed	1 / 482 (0.21%)	0 / 482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	0 / 482 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Attempted suicide			
subjects affected / exposed	1 / 482 (0.21%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychotic episode			
subjects affected / exposed	0 / 482 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Elevated creatine kinase			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 482 (0.41%)	4 / 482 (0.83%)	
occurrences causally related to treatment / all	2 / 2	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatotoxicity (raised ALT/AST)			
alternative assessment type: Systematic			
subjects affected / exposed	11 / 482 (2.28%)	4 / 482 (0.83%)	
occurrences causally related to treatment / all	11 / 11	5 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			

Fall			
subjects affected / exposed	12 / 482 (2.49%)	10 / 482 (2.07%)	
occurrences causally related to treatment / all	0 / 13	0 / 12	
deaths causally related to treatment / all	0 / 1	0 / 0	
Bone fracture			
subjects affected / exposed	12 / 482 (2.49%)	20 / 482 (4.15%)	
occurrences causally related to treatment / all	0 / 14	0 / 22	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dislocated Shoulder			
subjects affected / exposed	1 / 482 (0.21%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suprapubic catheter insertion complications			
subjects affected / exposed	0 / 482 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Traumatic head injury			
subjects affected / exposed	0 / 482 (0.00%)	2 / 482 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial Fibrillation			
subjects affected / exposed	2 / 482 (0.41%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Emergency surgery for enlarged aorta - valve inserted (Aorta Dissection)			
subjects affected / exposed	0 / 482 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			

subjects affected / exposed	0 / 482 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocarditis			
subjects affected / exposed	0 / 482 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Heart surgery for heart murmour			
subjects affected / exposed	0 / 482 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	1 / 482 (0.21%)	2 / 482 (0.41%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Angina			
subjects affected / exposed	0 / 482 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Functional decline due to progressive MS			
subjects affected / exposed	2 / 482 (0.41%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cauda equina syndrome			
subjects affected / exposed	1 / 482 (0.21%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	0 / 482 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Migraine			

subjects affected / exposed	1 / 482 (0.21%)	2 / 482 (0.41%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple Sclerosis relapse			
subjects affected / exposed	8 / 482 (1.66%)	6 / 482 (1.24%)	
occurrences causally related to treatment / all	0 / 8	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudorelapse			
subjects affected / exposed	1 / 482 (0.21%)	0 / 482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	3 / 482 (0.62%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stroke			
subjects affected / exposed	2 / 482 (0.41%)	3 / 482 (0.62%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subarachnoid haemorrhage			
subjects affected / exposed	1 / 482 (0.21%)	0 / 482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Transient ischemic attack			
subjects affected / exposed	1 / 482 (0.21%)	0 / 482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Essential Thrombocythemia			
subjects affected / exposed	1 / 482 (0.21%)	0 / 482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			

Vertigo			
subjects affected / exposed	2 / 482 (0.41%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vestibular neuritis			
subjects affected / exposed	0 / 482 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Emergency surgery for glaucoma			
subjects affected / exposed	1 / 482 (0.21%)	0 / 482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Macular hole repair left eye			
subjects affected / exposed	0 / 482 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Right retinal detachment			
subjects affected / exposed	0 / 482 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastric bleed			
subjects affected / exposed	0 / 482 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	2 / 482 (0.41%)	2 / 482 (0.41%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Crohn's Disease			
subjects affected / exposed	0 / 482 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Acute bowel obstruction			
subjects affected / exposed	1 / 482 (0.21%)	0 / 482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	0 / 482 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dental abscess			
subjects affected / exposed	0 / 482 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	1 / 482 (0.21%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	2 / 482 (0.41%)	0 / 482 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Entercolitis			
subjects affected / exposed	0 / 482 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroesophageal reflux disease			
subjects affected / exposed	1 / 482 (0.21%)	0 / 482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Partial intra-thoracic gastric volvus			
subjects affected / exposed	0 / 482 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			

Gallbladder removal			
subjects affected / exposed	0 / 482 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Bladder urgency			
subjects affected / exposed	1 / 482 (0.21%)	0 / 482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Kidney stone			
subjects affected / exposed	3 / 482 (0.62%)	0 / 482 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Emergency nephtostomy tube insertion			
subjects affected / exposed	1 / 482 (0.21%)	0 / 482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Phimosis			
subjects affected / exposed	0 / 482 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Severely reduced renal function			
subjects affected / exposed	1 / 482 (0.21%)	0 / 482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	2 / 482 (0.41%)	2 / 482 (0.41%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	1 / 482 (0.21%)	0 / 482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Secondary Adrenal Insufficiency			
subjects affected / exposed	0 / 482 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	1 / 482 (0.21%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decreased mobility			
subjects affected / exposed	1 / 482 (0.21%)	0 / 482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disc bulge			
subjects affected / exposed	0 / 482 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Divarification of rectus muscle			
subjects affected / exposed	0 / 482 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Knee surgery			
subjects affected / exposed	1 / 482 (0.21%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower back pain			
subjects affected / exposed	1 / 482 (0.21%)	0 / 482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular pain			
subjects affected / exposed	1 / 482 (0.21%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Metacarpophalangeal joint dislocation			
subjects affected / exposed	0 / 482 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhabdomyolysis			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 482 (0.21%)	0 / 482 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Clostridium difficile infection			
subjects affected / exposed	2 / 482 (0.41%)	0 / 482 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest infection			
subjects affected / exposed	2 / 482 (0.41%)	0 / 482 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19 infection			
subjects affected / exposed	7 / 482 (1.45%)	6 / 482 (1.24%)	
occurrences causally related to treatment / all	0 / 7	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	7 / 482 (1.45%)	2 / 482 (0.41%)	
occurrences causally related to treatment / all	0 / 10	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gastroenteritis			
subjects affected / exposed	2 / 482 (0.41%)	5 / 482 (1.04%)	
occurrences causally related to treatment / all	0 / 2	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected cyst			

subjects affected / exposed	1 / 482 (0.21%)	0 / 482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected pressure sore			
subjects affected / exposed	1 / 482 (0.21%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	0 / 482 (0.00%)	4 / 482 (0.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection of supra pubic catheter site			
subjects affected / exposed	0 / 482 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection to skin of thumb			
subjects affected / exposed	0 / 482 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periorbital cellulitis			
subjects affected / exposed	0 / 482 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	2 / 482 (0.41%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	2 / 482 (0.41%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shingles			

subjects affected / exposed	1 / 482 (0.21%)	0 / 482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	4 / 482 (0.83%)	7 / 482 (1.45%)	
occurrences causally related to treatment / all	0 / 5	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	16 / 482 (3.32%)	19 / 482 (3.94%)	
occurrences causally related to treatment / all	0 / 17	0 / 26	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	1 / 482 (0.21%)	0 / 482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	0 / 482 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatremia			
subjects affected / exposed	0 / 482 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	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	Simvastatin	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	427 / 482 (88.59%)	423 / 482 (87.76%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			

subjects affected / exposed	17 / 482 (3.53%)	21 / 482 (4.36%)	
occurrences (all)	24	24	
Vascular disorders			
Vascular disorders			
subjects affected / exposed	15 / 482 (3.11%)	22 / 482 (4.56%)	
occurrences (all)	16	24	
Surgical and medical procedures			
Surgical and medical procedures			
subjects affected / exposed	15 / 482 (3.11%)	7 / 482 (1.45%)	
occurrences (all)	16	7	
General disorders and administration site conditions			
General disorders and administration site conditions			
subjects affected / exposed	119 / 482 (24.69%)	128 / 482 (26.56%)	
occurrences (all)	164	179	
Immune system disorders			
Immune system disorders			
subjects affected / exposed	5 / 482 (1.04%)	9 / 482 (1.87%)	
occurrences (all)	5	9	
Reproductive system and breast disorders			
Reproductive system and breast disorders			
subjects affected / exposed	14 / 482 (2.90%)	22 / 482 (4.56%)	
occurrences (all)	16	22	
Respiratory, thoracic and mediastinal disorders			
Respiratory, thoracic and mediastinal disorders			
subjects affected / exposed	39 / 482 (8.09%)	32 / 482 (6.64%)	
occurrences (all)	46	55	
Psychiatric disorders			
Psychiatric disorders			
subjects affected / exposed	23 / 482 (4.77%)	26 / 482 (5.39%)	
occurrences (all)	27	27	
Investigations			
Investigations			
subjects affected / exposed	34 / 482 (7.05%)	24 / 482 (4.98%)	
occurrences (all)	42	26	
Injury, poisoning and procedural complications			

Injury, poisoning and procedural complications			
subjects affected / exposed	168 / 482 (34.85%)	157 / 482 (32.57%)	
occurrences (all)	303	265	
Cardiac disorders			
Cardiac disorders			
subjects affected / exposed	11 / 482 (2.28%)	17 / 482 (3.53%)	
occurrences (all)	11	16	
Nervous system disorders			
Nervous system disorders			
subjects affected / exposed	145 / 482 (30.08%)	136 / 482 (28.22%)	
occurrences (all)	210	226	
Blood and lymphatic system disorders			
Blood and lymphatic system disorders	Additional description: Events for Blood and lymphatic system disorders SOC		
subjects affected / exposed	11 / 482 (2.28%)	6 / 482 (1.24%)	
occurrences (all)	12	6	
Ear and labyrinth disorders			
Ear and labyrinth disorders			
subjects affected / exposed	30 / 482 (6.22%)	23 / 482 (4.77%)	
occurrences (all)	35	26	
Eye disorders			
Eye disorders			
subjects affected / exposed	25 / 482 (5.19%)	30 / 482 (6.22%)	
occurrences (all)	31	36	
Gastrointestinal disorders			
Gastrointestinal disorders			
subjects affected / exposed	105 / 482 (21.78%)	105 / 482 (21.78%)	
occurrences (all)	170	142	
Hepatobiliary disorders			
Hepatobiliary disorders			
subjects affected / exposed	6 / 482 (1.24%)	1 / 482 (0.21%)	
occurrences (all)	6	1	
Skin and subcutaneous tissue disorders			
Skin and subcutaneous tissue disorders			
subjects affected / exposed	68 / 482 (14.11%)	56 / 482 (11.62%)	
occurrences (all)	78	66	
Renal and urinary disorders			

Renal and urinary disorders			
subjects affected / exposed	25 / 482 (5.19%)	15 / 482 (3.11%)	
occurrences (all)	26	16	
Endocrine disorders			
Endocrine disorders			
subjects affected / exposed	5 / 482 (1.04%)	3 / 482 (0.62%)	
occurrences (all)	5	3	
Musculoskeletal and connective tissue disorders			
Musculoskeletal and connective tissue disorders			
subjects affected / exposed	157 / 482 (32.57%)	148 / 482 (30.71%)	
occurrences (all)	220	236	
Infections and infestations			
Infections and infestations			
subjects affected / exposed	279 / 482 (57.88%)	262 / 482 (54.36%)	
occurrences (all)	660	598	
Metabolism and nutrition disorders			
Metabolism and nutrition disorders			
subjects affected / exposed	9 / 482 (1.87%)	13 / 482 (2.70%)	
occurrences (all)	9	14	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 January 2018	Protocol update to v2.0 - Introduced a new exclusion criterion to prevent enrolment of patients with rare hereditary lactose-related disorders, add formal trial identifiers, and implement two additional fatigue questionnaires across all sites. It also establish three optional sub-studies (MRI, biomarker, and OCT), permit recruitment of healthy blood donors for the biomarker sub-study, and update procedures for obtaining consent and reporting serious events, including pregnancy notifications by male participants. Additional changes include switching from ABILHAND-56 to ABILHAND-23, updating oversight committee terminology, adding glossary terms, and making minor edits and formatting improvements throughout the protocol.
02 August 2018	Protocol update to v3.0 - Introduced updated branding and GDPR references, simplified and clarified inclusion criteria, and made broad refinements across governance, secondary outcomes, participant timelines, assessments, and operational procedures. It clarified eligibility, data collection processes, safety reporting, handling of intervention adherence, and follow-up procedures. Extensive updates were also made to the MRI, biomarker, and OCT sub-studies, including added eligibility criteria, clarified outcomes, and the addition of a new ABILHAND-23 sub-study.
22 July 2019	Protocol update to v4.0 - Updated exclusion criteria to include elbasvir, grazoprevir, recent cladribine, and to specify dimethyl fumarate, and corrected the primary outcome to reflect change in EDSS from baseline. Terminology was standardised, and laboratory-related sections were revised to add information on myopathy and clarify dose-modification strategies. Further updates refined contraindicated medications, the definition of trial end, and guidance for SLCVA testing and participant timelines, including limiting the FAB to a sub-study at UCLH and revising safety blood requirements. Safety reporting procedures were clarified, including updates to AE/SAE criteria and use of CTCAE V5, and adjustments were made to responsibilities for assessing expectedness. Additional changes included updating site maps, correcting references, expanding biomarker storage plans, refining OCT sub-study assessments, and adding a new FAB sub-study appendix.
23 March 2020	Protocol update to v5.0 - Clarified the schedule for safety blood testing, specifying that assessments would occur at Month 1 (40 mg tolerance), Month 3 (80 mg tolerance), and then at least annually from Month 6 to Month 36. It stated that patients unable to attend the Month 3 high-dose assessment should be de-escalated to 40 mg and re-challenged later if clinically appropriate. Once stable on the 80 mg dose, annual testing was considered sufficient unless clinical need required more frequent monitoring. It also established that no additional IMP would be dispensed if more than 12 months had passed since the last safety blood evaluation.
11 August 2020	Protocol update to v6.0 - Clarified the minimum required interval since an MS relapse for eligibility and added Ticagrelor and Daptomycin as exclusion and contraindicated medications, with related updates to laboratory abnormality guidance and dose re-challenge procedures. It allowed, in exceptional circumstances such as COVID-19, the combining of screening and baseline visits and permitted the Month 1 visit to be conducted remotely. Guidance on loss to follow-up was expanded to include categories of participation, and the map of expected MS-STAT2 sites was updated.

17 February 2021	Protcol update to v7.0 - updated the structured summary, trial team details, abbreviations, glossary and trial diagrams to reflect new protocol processes and definitions. It redefined the trial aim to assess whether disability progression could be slowed over the treatment period (rather than 3 years as previously), and revised the primary and secondary objectives and outcomes to include the additional trial visits, including clarification of EDSS comparisons and a shift to analysing the proportion of progression events. The design was amended to allow 1–3 additional six-monthly visits after Month 36 for patients without a confirmed progression event, with accompanying updates to the treatment schedule, participant timeline and processes for determining whether additional visits were required. Sample size calculations were revised, reducing the target sample due to recruitment impacts, and statistical methods were updated, including a new censor point for the primary outcome and changes to secondary outcome modelling. Finally, the analysis population description was updated to confirm that adherence would be assessed until each patient's final visit.
26 February 2024	Protocol update to v8.0 - Updated the structured summary, staffing information, and background section to incorporate current prevalence data, cost estimates, limited UK use of Siponimod, and recent research on statin mechanisms. It removed the option for a 3–6-month confirmatory visit after an initial progression at Visit 10 so that all visits were treated consistently, as this had been updated within the previous amendment with the addition of vists 11-13, with corresponding wording removed across relevant sections. Additional detail was provided for secondary objectives, statistical subgroup analyses related to COVID-19, and outcome analysis methods, including corrections to terminology and clarification of health economic analyses. Expectations for in-person assessments at Baseline and Visit 10 were clarified, Figure 2 was updated to reflect final site selection, and the MRI sub-study was revised to include QSM and MTV advanced imaging techniques.

Notes:

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/39284697

http://www.ncbi.nlm.nih.gov/pubmed/41045938

http://www.ncbi.nlm.nih.gov/pubmed/35945550

http://www.ncbi.nlm.nih.gov/pubmed/40631687