Clinical trial results:
A double-blind, randomised, placebo-controlled single-site study of high dose simvastatin treatment for secondary progressive multiple sclerosis: impact on vascular perfusion and oxidative damage

Summary

EudraCT number	2017-003008-30
Trial protocol	GB
Global end of trial date	15 June 2023

Results information

Result version number	v1 (current)
This version publication date	26 November 2025
First version publication date	26 November 2025

Trial information

Trial identification

Sponsor protocol code	16/0730

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03896217
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University College London
Sponsor organisation address	250 Euston Road, London, United Kingdom, NW1 2PG
Public contact	Richard Nicholas, University College London , ctimps@ucl.ac.uk
Scientific contact	Richard Nicholas, University College London , ctimps@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	06 December 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 September 2022
Global end of trial reached?	Yes
Global end of trial date	15 June 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Primary objective: To establish whether simvastatin has an effect on cerebral blood flow in progressive MS over 20 weeks using arterial spin labelling MRI.

Secondary objectives:
• To establish whether ASL and AOSLO measurements of blood flow are useful correlates for cerebral blood flow measurement on and off treatment.
• To explore whether statin could influence conventional and advanced MRI measures.
• To examine the clinical effect of simvastatin treatment as reported by the clinician and and patient reported
outcome measures.
• To investigate the effect statins on retinal parameters such as blood flow, oxygen saturation, structure of vascular plexuses, neuronal structure and retinal layer thicknesses.

Exploratory objectives:
• To investigate phenotypic immune markers in whole blood to determine effect simvastatin has on immune function.
• To measure the effect of statins on biomarkers of blood brain barrier dysfunction, vascular leakage and oxidative damage.

Protection of trial subjects:

To protect participants and minimise pain or distress during the MS-OPT trial, a range of carefully designed safety and comfort measures were implemented. Eligibility screening was rigorous, including clinical, laboratory, and MRI safety assessments, to exclude individuals at higher risk of adverse effects from simvastatin. Participants with recent MS relapses, contraindicated medications, or significant liver, kidney, or cardiac issues were not enrolled. Throughout the trial, participants underwent regular monitoring, including blood tests for liver function and creatine kinase levels, allowing early detection of hepatotoxicity or myopathy.

Importantly, to reduce travel burden and physical strain — particularly given participants' disability levels — study visits were split across two days and conducted at two different specialist centres: UCL Queen Square and Moorfields Eye Hospital. This approach ensured that no single visit became overly long or exhausting.

In addition, advanced imaging procedures such as MRI and retinal scans were only conducted with participants able to tolerate them, and clear exclusions (e.g. for metal implants or claustrophobia) were in place.

Retinal imaging involved pupil dilation using single-use sterile drops, with patients advised to bring sunglasses to ease post-visit discomfort. Venepuncture was carried out using standard precautions by trained staff to minimise discomfort and risk.

Participants were well-informed about possible side effects through detailed written information provided in the Participant Information Sheet, which was discussed thoroughly during the informed consent process. Participants were well-informed about possible side effects, encouraged to report symptoms promptly, and supported throughout the trial. These combined measures helped ensure a safe, ethical, and participant-centred study experience.

Background therapy:

Simvastatin is a widely used HMG-CoA reductase inhibitor, traditionally prescribed to lower LDL cholesterol and reduce cardiovascular risk. Beyond lipid regulation, simvastatin shows pleiotropic effects — immunomodulatory, anti-inflammatory, and vasculoprotective — which support its potential use in

multiple sclerosis (MS). In progressive MS (PMS), disease progression is driven more by microglial activation, mitochondrial dysfunction, oxidative damage, and vascular insufficiency than by acute inflammation. Simvastatin may counter these through enhancing endothelial nitric oxide synthase (eNOS), inhibiting iNOS, reducing pro-inflammatory cytokines, and modulating leukocyte-endothelial interactions.
Preclinical studies have shown that statins can reduce leukocyte infiltration across the blood-brain and blood-retinal barriers by interfering with Rho prenylation and endothelial cell signalling. Furthermore, in animal models of MS, simvastatin has been shown to attenuate disease severity by reducing oxidative stress and preserving vascular function. Clinically, a previous Phase II double-blind, placebo-controlled trial conducted by the same investigator group demonstrated that high-dose simvastatin (80 mg daily) led to a significant 43% reduction in the rate of brain atrophy in individuals with SPMS, alongside favourable trends in disability progression. Interestingly, this study found no significant changes in immune markers, suggesting that the benefits of simvastatin may not be mediated through traditional immunosuppression but rather through neuroprotective and vasoprotective mechanisms.
The MS-OPT trial was thus designed to explore these mechanisms. It assesses whether high-dose simvastatin improves cerebral and retinal perfusion, reduces oxidative damage, and protects neuroaxonal integrity in progressive MS. Advanced imaging and biomarker analyses will help clarify its mode of action and support its potential repositioning for this under-treated phase of MS.

Evidence for comparator:

The comparator in the MS-OPT trial is a matched placebo, formulated to be visually identical to simvastatin capsules to maintain double-blinding. The placebo tablets consist of gelatin and microcrystalline cellulose and do not contain any pharmacologically active ingredients. Participants randomised to the placebo arm follow the same dosing schedule as those receiving simvastatin: one tablet daily for four weeks, followed by two tablets daily for the remaining 17-week treatment period. Importantly, at the time this trial was conducted, there were no specific disease-modifying treatments approved for secondary progressive multiple sclerosis (SPMS), making the use of a placebo both ethically and scientifically appropriate. The placebo control enables a clear assessment of simvastatin’s effects by accounting for the natural course of disease progression and eliminating bias due to participant or investigator expectations. All participants — whether receiving simvastatin or placebo — underwent identical safety monitoring, clinical assessments, and support procedures, ensuring ethical parity and high-quality data collection across both trial arms.

Actual start date of recruitment	19 June 2019
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: 40
Worldwide total number of subjects	40
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 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	37
From 65 to 84 years	3
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The MS-OPT trial recruited 40 participants with SPMS or PPMS, aged 18 and over, with EDSS scores between 4.0 and 6.5 and evidence of steady progression. Recruitment took place at a single site split across UCL Queen Square and Moorfields Eye Hospital, with visits coordinated between both locations.

Pre-assignment

Screening details:

Screening included medical history, physical exam, EDSS assessment, blood tests (including liver and kidney function, CK), ECG, and MRI safety checks. Participants also underwent review of prior MS progression and current medications to confirm eligibility and ensure no contraindications to simvastatin.

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, Carer, Assessor

Blinding implementation details:

The MS-OPT trial was double-blind, meaning neither participants nor investigators knew the treatment allocation. Simvastatin and placebo tablets were identical in appearance and packaging, prepared by a third-party manufacturer. Randomisation was managed using a secure minimisation algorithm, and all study procedures, including dosing and assessments, were conducted identically across both arms to maintain blinding integrity.

Arms

Are arms mutually exclusive?	Yes
Arm title	Simvastatin

Arm description:

Participants randomised to the simvastatin arm received oral simvastatin starting at a dose of 40 mg once daily in the evening for the first four weeks. Following a satisfactory safety review, the dose was increased to 80 mg daily (administered as two 40 mg capsules) for the remaining 13 weeks of the 17-week treatment period. Simvastatin was over-encapsulated to match the placebo in appearance, maintaining the integrity of the double-blind design. Participants were advised to take the medication at a consistent time each evening, with or without food, and were monitored regularly for safety through blood tests and clinical assessments. Adherence was reinforced through medication diaries and pill counts. Dose adjustments or discontinuation were allowed if clinically indicated due to adverse effects or lab abnormalities.

Arm type	Experimental
Investigational medicinal product name	Simvastatin
Investigational medicinal product code	ATC-Code: C10A A01
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

In the MS-OPT trial, simvastatin was administered orally at a high dose, following a structured titration schedule to enhance tolerability. Participants assigned to the active treatment arm received 40 mg once daily in the evening for the first four weeks. After a satisfactory safety assessment at Week 4, the dose was increased to 80 mg once daily for the remaining 13 weeks of the 17-week treatment period. Simvastatin and placebo tablets were over-encapsulated to ensure visual indistinguishability and preserve blinding. Participants were instructed to take the medication with water in the evening and maintain consistent timing throughout the study. Adherence was supported through the use of medication diaries and pill counts at each visit. Dose modifications or discontinuation were permitted at the discretion of the treating clinician if adverse effects occurred. All participants received clear guidance on how to take the medication and were monitored regularly for safety throughout th

Arm title	Placebo

Arm description:

Participants in the placebo arm received capsules containing an inert substance (gelatin and microcrystalline cellulose), matched in appearance and dosing schedule to the active treatment. Like the simvastatin arm, dosing began with one capsule daily for the first four weeks, increasing to two capsules daily for the remaining 13 weeks. All procedures, including monitoring, assessments, and participant instructions, were identical to those in the simvastatin arm to preserve blinding and ensure consistent data collection. The use of placebo was considered ethically appropriate, as no approved disease-modifying treatments for secondary progressive MS were available at the time of the trial. This design allowed for a rigorous evaluation of simvastatin's effects while ensuring participant safety and trial integrity.

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:

Participants randomised to the placebo arm received visually identical capsules containing inactive ingredients—gelatin and microcrystalline cellulose. The dosing schedule matched that of the simvastatin arm to maintain blinding and ensure consistency. Participants began with one placebo capsule (equivalent to 40 mg simvastatin in appearance) taken once daily in the evening for the first four weeks. Following this initial phase, and provided no safety concerns were identified, the dose was increased to two placebo capsules daily (equivalent in appearance to 80 mg simvastatin) for the remaining 13 weeks of the 17-week treatment period. Capsules were taken orally with water, preferably at the same time each evening. Participants were instructed to maintain adherence using a medication diary and to return unused capsules at follow-up visits for compliance checks. All procedures, including safety monitoring and clinical assessments, were identical to those in the simvastatin arm.

Number of subjects in period 1	Simvastatin	Placebo
Started	20	20
Completed	19	20
Not completed	1	0
Lost to follow-up	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Simvastatin

Reporting group description:

Participants randomised to the simvastatin arm received oral simvastatin starting at a dose of 40 mg once daily in the evening for the first four weeks. Following a satisfactory safety review, the dose was increased to 80 mg daily (administered as two 40 mg capsules) for the remaining 13 weeks of the 17-week treatment period. Simvastatin was over-encapsulated to match the placebo in appearance, maintaining the integrity of the double-blind design. Participants were advised to take the medication at a consistent time each evening, with or without food, and were monitored regularly for safety through blood tests and clinical assessments. Adherence was reinforced through medication diaries and pill counts. Dose adjustments or discontinuation were allowed if clinically indicated due to adverse effects or lab abnormalities.

Reporting group title	Placebo

Reporting group description:

Participants in the placebo arm received capsules containing an inert substance (gelatin and microcrystalline cellulose), matched in appearance and dosing schedule to the active treatment. Like the simvastatin arm, dosing began with one capsule daily for the first four weeks, increasing to two capsules daily for the remaining 13 weeks. All procedures, including monitoring, assessments, and participant instructions, were identical to those in the simvastatin arm to preserve blinding and ensure consistent data collection. The use of placebo was considered ethically appropriate, as no approved disease-modifying treatments for secondary progressive MS were available at the time of the trial. This design allowed for a rigorous evaluation of simvastatin’s effects while ensuring participant safety and trial integrity.

Reporting group values	Simvastatin	Placebo	Total
Number of subjects	20	20	40
Age categorical			
Measure Analysis Population Description: Forty patients, including 12 primary progressive MS and 28 secondary progressive MS, aged 18-70 years, and presenting with an Expanded Disability Status Scale (EDSS) score 4.0-6.5 were randomly assigned (1:1) to Simvastatin 80 mg or placebo for 16 weeks.			
Units: Subjects			
Adults (18-64 years)	19	18	37
From 65-84 years	1	2	3
Age continuous			
Measure Analysis Population Description: Forty patients, including 12 primary progressive MS and 28 secondary progressive MS, aged 18-70 years, and presenting with an Expanded Disability Status Scale (EDSS) score 4.0-6.5 were randomly assigned (1:1) to Simvastatin 80 mg or placebo for 16 weeks.			
Units: years			
arithmetic mean	55.30	52.95	
standard deviation	± 7.51	± 9.48	-
Gender categorical			
Measure Analysis Population Description: Forty patients, including 12 primary progressive MS and 28 secondary progressive MS, aged 18-70 years, and presenting with an Expanded Disability Status Scale (EDSS) score 4.0-6.5 were randomly assigned (1:1) to Simvastatin 80 mg or placebo for 16 weeks.			
Units: Subjects			
Female	14	13	27
Male	6	7	13
Race (NIH/OMB)			
Measure Analysis Population Description: Forty patients, including 12 primary progressive MS and 28 secondary progressive MS, aged 18-70 years, and presenting with an Expanded Disability Status Scale (EDSS) score 4.0-6.5 were randomly assigned (1:1) to Simvastatin 80 mg or placebo for 16 weeks.			
Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	1	1

Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	1	1
White	20	18	38
More than one race	0	0	0
Unknown or Not Reported	0	0	0
Multiple Sclerosis Clinical Phenotype			
Measure Description: Clinical course at onset according to Lublin criteria			
Units: Subjects			
Primary Progressive Multiple Sclerosis	6	6	12
Secondary Progressive Multiple Sclerosis	14	14	28

End points

End points reporting groups

Reporting group title	Simvastatin

Reporting group description:

Participants randomised to the simvastatin arm received oral simvastatin starting at a dose of 40 mg once daily in the evening for the first four weeks. Following a satisfactory safety review, the dose was increased to 80 mg daily (administered as two 40 mg capsules) for the remaining 13 weeks of the 17-week treatment period. Simvastatin was over-encapsulated to match the placebo in appearance, maintaining the integrity of the double-blind design. Participants were advised to take the medication at a consistent time each evening, with or without food, and were monitored regularly for safety through blood tests and clinical assessments. Adherence was reinforced through medication diaries and pill counts. Dose adjustments or discontinuation were allowed if clinically indicated due to adverse effects or lab abnormalities.

Reporting group title	Placebo

Reporting group description:

Participants in the placebo arm received capsules containing an inert substance (gelatin and microcrystalline cellulose), matched in appearance and dosing schedule to the active treatment. Like the simvastatin arm, dosing began with one capsule daily for the first four weeks, increasing to two capsules daily for the remaining 13 weeks. All procedures, including monitoring, assessments, and participant instructions, were identical to those in the simvastatin arm to preserve blinding and ensure consistent data collection. The use of placebo was considered ethically appropriate, as no approved disease-modifying treatments for secondary progressive MS were available at the time of the trial. This design allowed for a rigorous evaluation of simvastatin’s effects while ensuring participant safety and trial integrity.

Primary: Effect on Cerebral Blood Flow in White Matter, Gray Matter, Deep White Matter, Deep Gray Matter, and Thalamus

End point title	Effect on Cerebral Blood Flow in White Matter, Gray Matter, Deep White Matter, Deep Gray Matter, and Thalamus

End point description:

To compare patients on simvastatin or placebo using multiple linear regressions. ASL is an MRI method that allows non-invasive measurement of CBF using inversion of arterial water spins as a tracer.The aim is to explore whether subtle changes in CBF occur over time between placebo and simvastatin treated patients, including potential waning of the effects of the drug over time.

End point type	Primary

End point timeframe:

At week 16

End point values	Simvastatin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	20		
Units: Percentage of change in CBF				
arithmetic mean (confidence interval 95%)				
White matter	8.55 (-1.63 to 14.77)	5.12 (-4.52 to 14.77)		
Gray matter	5.78 (-2.13 to 13.69)	2.06 (-5.43 to 9.54)		
Deep white matter	8.39 (-2.55 to 19.33)	6.69 (-3.67 to 17.05)		

Deep gray matter	7.33 (-1.20 to 15.85)	2.77 (-5.07 to 10.61)		
Thalamus	4.55 (-5.11 to 14.21)	-1.02 (-9.91 to 7.86)		

Statistical analyses

Statistical analysis title	Effect of simvastatin on Cerebral Blood Flow

Statistical analysis description:

To compare patients on simvastatin or placebo using multiple linear regressions. ASL is an MRI method that allows non-invasive measurement of CBF using inversion of arterial water spins as a tracer.The aim is to explore whether subtle changes in CBF occur over time between placebo and simvastatin treated patients, including potential waning of the effects of the drug over time.

Comparison groups	Simvastatin v Placebo
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05 [1]
Method	Regression, Linear

Notes:

[1] - The difference in mean percentage change at visit 3 was 3.43 (p=0.627) for white matter CBF, 3.72 (p=0.499) for grey matter CBF, 1.70 (p=0.822) for deep white matter CBF, 4.56 (p=0.435) for deep grey matter CBF, and 5.57 (p=0.400) for thalamus.

Primary: AOSLO Measurements of Blood Flow

End point title	AOSLO Measurements of Blood Flow

End point description:

To establish if Adaptive Optics Scanning Laser Ophthalmoscope (AOSLO) measurements of blood flow are useful correlates for cerebral blood flow measurement on and off treatment.

End point type	Primary

End point timeframe:

At week 16

End point values	Simvastatin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	17		
Units: Percentage of change				
arithmetic mean (confidence interval 95%)	0.87 (-15.12 to 16.86)	5.89 (-10.11 to 21.88)		

Statistical analyses

Statistical analysis title	AOSLO Measurements of Blood Flow

Statistical analysis description:

To establish if Adaptive Optics Scanning Laser Ophthalmoscope (AOSLO) measurements of blood flow are useful correlates for cerebral blood flow measurement on and off treatment.

Comparison groups	Simvastatin v Placebo

Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.66
Method	Regression, Linear

Secondary: MRI: ASL in White Matter, Gray Matter, Deep White Matter, Deep Gray Matter, and Thalamus

End point title	MRI: ASL in White Matter, Gray Matter, Deep White Matter, Deep Gray Matter, and Thalamus

End point description:

To evaluate whether ASL is useful correlate for cerebral blood flow measurement on and off treatment.

End point type	Secondary

End point timeframe:

At baseline

End point values	Simvastatin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	20		
Units: mL/100 g/min				
arithmetic mean (standard deviation)				
White matter	27.38 (± 8.30)	25.89 (± 7.56)		
Gray matter	76.82 (± 18.02)	70.78 (± 15.74)		
Deep White Matter	24.95 (± 7.74)	23.26 (± 7.56)		
Deep Gray Matter	46.33 (± 11.95)	44.72 (± 11.27)		
Thalamus	54.96 (± 17.52)	51.22 (± 13.75)		

Statistical analyses

No statistical analyses for this end point

Secondary: AOSLO Blood Flow Dynamics

End point title	AOSLO Blood Flow Dynamics

End point description:

AOSLO of retinal capillary microvessels was applied to calculate retinal perfusion and measure blood flow dynamics at the capillary level. We measured relative venous and artery blood pO2 levels near the optic nerve (central 3 disk diameters) to obtain vessel width and velocity.

End point type	Secondary

End point timeframe:

Over 16 weeks

End point values	Simvastatin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	18		
Units: Percentage of change				
arithmetic mean (confidence interval 95%)				
Vessel width	-3.04 (-15.93 to 9.84)	-2.64 (-14.76 to 9.48)		
Velocity	-13.40 (-25.50 to 1.29)	5.37 (-7.10 to 17.84)		

Statistical analyses

No statistical analyses for this end point

Secondary: MRI: Brain Atrophy

End point title	MRI: Brain Atrophy

End point description:

To explore whether statin reduce the rate of brain atrophy, including grey matter volumes, on MRI (excluding the effect of pseudo-atrophy, which is a temporary response to the drug rather than an actual loss of tissue). The MRI images will be analysed using softwares developed at UCL to quantify the amount of brain tissue loss over time.

End point type	Secondary

End point timeframe:

At week 16

End point values	Simvastatin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	20		
Units: Percentage of change				
arithmetic mean (confidence interval 95%)				
White Matter	-0.21 (-0.79 to 0.36)	0.14 (-1.17 to 0.46)		
Gray Matter	-0.32 (-0.74 to 0.09)	-0.19 (-0.58 to 0.20)		
Cortical Gray Matter	-0.32 (-0.75 to 0.10)	-0.20 (-0.60 to 0.20)		
Hippocampus	-0.51 (-1.11 to 0.09)	-0.44 (-1.00 to 0.13)		
Thalamus	-0.25 (-0.91 to 0.42)	-0.04 (-0.67 to 0.59)		
Pallidum	0.15 (-0.79 to 1.09)	-0.68 (-1.57 to 0.21)		
Putamen	-0.30 (-0.80 to 0.21)	-0.85 (-1.34 to -0.38)		

Ventral diencephalon	0.09 (-0.48 to 0.66)	-0.85 (-1.39 to 0.32)		

Statistical analyses

No statistical analyses for this end point

Secondary: MRI: Diffusion Tensor Imaging (DTI)

End point title	MRI: Diffusion Tensor Imaging (DTI)

End point description:

Diffusion weighted imaging (DWI) is an MR imaging technique based upon the measurement of the random Brownian motion of water within a voxel of tissue. This technique has been used to analyse the microstructure of neuronal tissue in particular myelin and axonal integrity. Data are reported for white matter

End point type	Secondary

End point timeframe:

At week 16

End point values	Simvastatin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	19		
Units: Percentage of change				
arithmetic mean (confidence interval 95%)				
Fractional anisotropy (FA)	-0.01 (-0.95 to 0.92)	-0.22 (-1.14 to 0.69)		
Mean diffusivity (MD)	1.13 (0.01 to 2.26)	0.31 (-0.78 to 1.40)		

Statistical analyses

No statistical analyses for this end point

Secondary: MRI: Neurite Density and Orientation Dispersion Imaging

End point title	MRI: Neurite Density and Orientation Dispersion Imaging

End point description:

To assess changes in axonal parameters, such as fiber orientation dispersion and axonal densities occurring over time using NODDI, an advanced MRI technique that reflects the microstructural complexity of dendrites and axons in vivo. Data are reported for white matter.

End point type	Secondary

End point timeframe:

At week 16

End point values	Simvastatin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	19		
Units: Percentage of change				
arithmetic mean (confidence interval 95%)				
Intra-neurite volume fraction	-1.27 (-2.58 to 0.04)	-0.48 (-1.75 to 0.79)		
Isotropic volume fraction	2.45 (-0.58 to 5.47)	-0.12 (-3.06 to 2.83)		

Statistical analyses

No statistical analyses for this end point

Secondary: MRI: MTV

End point title	MRI: MTV

End point description:

Macromolecular tissue volume (MTV) is a method of myelin mapping to determine the role of myelin loss or changes in progressive MS. With the macromolecular volume being made up of 50% myelin, we are able to use an in-house analysis pipeline to calculate the MTV - a surrogate marker of brain myelin volume. This metric, alongside diffusion weighted imaging will provide micro-structural detail into the cross-sectional and longitudinal changes occurring in the brain parenchyma of people with progressive MS.

End point type	Secondary

End point timeframe:

At week 16

End point values	Simvastatin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	19		
Units: Percentage of change				
arithmetic mean (confidence interval 95%)				
Cortical Gray Matter	3.65 (-8.29 to 15.59)	7.30 (-4.30 to 18.89)		
Deep Gray Matter	-2.27 (-7.31 to 2.77)	1.89 (-3.01 to 6.79)		
Normal-Appearing White Matter	-0.68 (-4.72 to 3.36)	1.77 (-2.15 to 5.70)		
Brainstem	-1.69 (-7.22 to 3.83)	1.71 (-3.65 to 7.08)		
Lesions	-2.12 (-7.79 to 3.56)	2.66 (-2.86 to 8.17)		

Statistical analyses

No statistical analyses for this end point

Secondary: OCT-A: Retinal Nerve Fibre Layer

End point title	OCT-A: Retinal Nerve Fibre Layer

End point description:

Inner retinal thickness will be measured using optical coherence tomography (OCT). OCT is a method of retinal imaging which is non-invasive and involves the patient holding their head still and staring at a dim light while imaging takes place. Peripapillary retinal nerve fibre layer (pRNFL) thickness is a strong candidate as a biomarker of axonal degeneration in MS.

End point type	Secondary

End point timeframe:

At week 16

End point values	Simvastatin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	18		
Units: Percentage of change				
arithmetic mean (confidence interval 95%)	2.28 (-0.08 to 4.64)	-0.29 (-2.52 to 1.93)		

Statistical analyses

No statistical analyses for this end point

Secondary: OCT-A: Vessel Density

End point title	OCT-A: Vessel Density

End point description:

OCT-A images will be processed to produce quantitative data of perfusion indices. Vessel density (VD) is defined as the "percentage area occupied by vessels in the segmented area.

End point type	Secondary

End point timeframe:

At week 16

End point values	Simvastatin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	19		
Units: Percentage of change				
arithmetic mean (confidence interval 95%)	7.59 (-11.12 to 26.30)	15.15 (-1.97 to 32.26)		

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Outcome: EDSS

End point title	Clinical Outcome: EDSS

End point description:

To examine the clinical effect of simvastatin treatment as reported by the clinician. Clinician observed expanded disability status score (EDSS) is a method of quantifying disability in MS and records changes in disability over time. The EDSS scale ranges from 0 (no disability) to 10 (death due to MS) in 0.5 unit increments that represent higher levels of disability. Scoring is based on an examination by a neurologist and encompasses pyramidal, cerebellar, brainstem, sensory, bowel/bladder function in addition to visual, cerebral and other functions. Mean change from baseline to visit 3 is reported.

End point type	Secondary

End point timeframe:

At week 16

End point values	Simvastatin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	20		
Units: units on a scale				
arithmetic mean (confidence interval 95%)	-0.19 (-0.46 to 0.08)	0.04 (-0.21 to 0.30)		

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Outcomes: MSFC: 25 Foot Timed Walk

End point title	Clinical Outcomes: MSFC: 25 Foot Timed Walk

End point description:

To examine the clinical effect of simvastatin treatment as reported by the clinician . Multiple Sclerosis Function Composite (MSFC) includes the 25 foot timed foot walk (25TFW), which involves marking a 25-foot distance in an unobstructed hallway; an assistive device (if needed) may be used by the participant and recorded. Their speed is then timed up to a time limit of 3 mins in both directions. Mean change from baseline to visit 3 is reported.

End point type	Secondary

End point timeframe:

At week 16

End point values	Simvastatin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	20		
Units: Seconds				
arithmetic mean (confidence interval 95%)	0.74 (-6.94 to 8.41)	2.37 (-4.90 to 9.64)		

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Outcomes: MSFC: 9 Hole Peg Test

End point title	Clinical Outcomes: MSFC: 9 Hole Peg Test

End point description:

To examine the clinical effect of simvastatin treatment as reported by the clinician. Multiple Sclerosis Function Composite (MSFC) includes the 9 hole peg test (9HPT). The 9-HPT is a quantitative measure of upper extremity (arm and hand) function. Both the dominant and non-dominant hands are tested twice (two consecutive trials of the dominant hand, followed immediately by two consecutive trials of the non-dominant hand). It is important that the 9-HPT be administered on a solid table (not a rolling hospital bedside table) and that the 9-HPT apparatus be anchored (e.g., with Dycem). The pegs are selected one at a time, using one hand only, and put into the holes as quickly as possible in any order until all the holes are filled. Then, without pausing, the pegs are removed one at a time and returned to the container. Mean change from baseline to visit 3 is reported.

End point type	Secondary

End point timeframe:

At week 16

End point values	Simvastatin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	20		
Units: Seconds				
arithmetic mean (confidence interval 95%)				
Dominant hand	-0.77 (-13.63 to 12.09)	4.51 (-7.65 to 16.68)		
Non-dominant hand	0.78 (-7.66 to 9.22)	-0.10 (-8.10 to 7.89)		

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Outcomes: SDMT

End point title	Clinical Outcomes: SDMT

End point description:

Symbol Digit Modalities Test (SDMT) is measure of cognitive impairment. The subject is asked to match single digits to symbols using a key as a guide that pairs the numbers to the symbols. They are presented with a page headed by a key that pairs the single digits 1-9 with nine symbols and they then write or orally report their responses in a scoring form. It can be administered in oral and written form and is timed and guided by a trained examiner ie. suitably qualified member of the research team. Changes in scores were recorded over the time-points described. Scores range from 0 to 110, with higher scores indicating better cognitive functioning. Mean change from baseline to visit 3 is reported.

End point type	Secondary

End point timeframe:

At week 16

End point values	Simvastatin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	20		
Units: Units on a scale				
arithmetic mean (confidence interval 95%)	-2.34 (-5.94 to 1.25)	0.01 (-3.40 to 3.42)		

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Outcomes: Frontal Executive Functioning: FAB

End point title	Clinical Outcomes: Frontal Executive Functioning: FAB

End point description:

Frontal Assessment Battery (FAB). The FAB is a brief tool that can be used at the bedside or in a clinic setting to assist in discriminating between dementias with a frontal dysexecutive phenotype and dementia of Alzheimer"s Type (DAT). The FAB has validity in distinguishing Fronto-temporal type dementia from DAT in mildly demented patients (MMSE > 24). Total score is from a maximum of 18, higher scores indicating better performance. Changes in scores were recorded over the time-points described. The FAB evaluates executive functions through six subtests, including conceptualization, mental flexibility, motor programming, sensitivity to interference, inhibitory control, and environmental autonomy. Each subtest is scored from 0 to 3, yielding a total score range of 0 to 18. Higher scores indicate better executive functioning. The total score is calculated by summing the six subtest scores. Mean change from baseline to visit 3 is reported.

End point type	Secondary

End point timeframe:

At week 20

End point values	Simvastatin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	19		
Units: Units on a scale				
arithmetic mean (confidence interval 95%)	0.38 (-0.24 to 1.00)	0.40 (-0.22 to 1.03)		

Statistical analyses

No statistical analyses for this end point

Secondary: Patient-Reported Outcomes: MSIS-29v2 Questionnaires

End point title	Patient-Reported Outcomes: MSIS-29v2 Questionnaires

End point description:

To examine the clinical effect of simvastatin treatment as reported by patient reported outcome measures. Patient reported multiple sclerosis impact scale version 2 (MSIS-29v2) is a self-administered questionnaire covering 29 items that asks to what degree MS has impacted the person physically and mentally over the past two weeks. It consists of 29 items divided into two subscales: Physical Impact (20 items; score range: 20-100) and Psychological Impact (9 items; score range: 9-45). Each item is rated on a 5-point Likert scale. Higher scores reflect a greater negative impact of MS on the individual's quality of life. Mean change from baseline to visit 3 is reported.

End point type	Secondary

End point timeframe:

At week 16

End point values	Simvastatin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	20		
Units: Units on a scale				
arithmetic mean (confidence interval 95%)				
Physical impact	1.08 (-4.53 to 6.69)	-5.09 (-10.39 to 0.20)		
Psychological impact	1.54 (-5.11 to 8.19)	1.81 (-4.48 to 8.10)		

Statistical analyses

No statistical analyses for this end point

Secondary: Patient-Reported Outcomes: MSWT-12V2 Questionnaires

End point title	Patient-Reported Outcomes: MSWT-12V2 Questionnaires

End point description:

Patient reported Multiple Sclerosis Walking Test version 2 (MSWT-12V2) is a 12 item self-administered questionnaire that measures walking performance over the previous two weeks. Each items is summed to generate a total score which is then transformed to a scale ranging from 0 to 100. Higher scores indicate greater impact on walking. Mean change from baseline to visit 3 is reported.

End point type	Secondary

End point timeframe:

At week 16

End point values	Simvastatin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	19		
Units: Units on a scale				
arithmetic mean (confidence interval 95%)	1.43 (-3.64 to 6.31)	3.15 (-1.46 to 7.77)		

Statistical analyses

No statistical analyses for this end point

Secondary: Health Economic Outcomes: EQ5D5L

End point title	Health Economic Outcomes: EQ5D5L

End point description:

The EuroQol Health-Related Quality of Life (EQ-5D-5L) is a standardized instrument for assessing health-related quality of life across five domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each domain is rated on a five-level scale, ranging from 1 (no problems) to 5 (extreme problems). The EQ-5D-5L also includes a visual analogue scale (VAS), on which individuals rate their overall health from 0 (worst imaginable health state) to 100 (best imaginable health state). Results are reported as the mean change in domain scores and VAS ratings from baseline to Visit 3.

End point type	Secondary

End point timeframe:

At week 16

End point values	Simvastatin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	20		
Units: Units on a scale				
arithmetic mean (confidence interval 95%)				
Mobility	0.11 (-0.09 to 0.32)	0.20 (0.001 to 0.39)		
Self-care	-0.09 (-0.39 to 0.20)	-0.07 (-0.35 to 0.21)		
Usual activities	0.15 (-0.18 to 0.49)	0.11 (-0.21 to 0.43)		
Pain/discomfort	0.25 (-0.06 to 0.55)	0.18 (-0.11 to 0.46)		
Anxiety/depression	-0.08 (-0.42 to 0.27)	0.07 (-0.26 to 0.39)		
VAS	4.20 (-1.41 to 9.81)	2.07 (-3.25 to 7.39)		

Statistical analyses

No statistical analyses for this end point

Secondary: Immune Parameters, and Biomarkers

End point title	Immune Parameters, and Biomarkers

End point description:

Blood samples from these patients will be taken at baseline and at weeks 4, 16 and 20 to investigate the effect of statins on vascular leakage and free radical damage. Biomarkers will be determined as follows: (i) For RNA/DNA oxidative damage serum levels of 8-hydroxyguanosine (8-OHG)/8-hydroxydeoxyguanosine (8-OHdG); (ii) Protein oxidative damage will be determined by assaying plasma proteins for nitrotyrosine and carbonyl content; and (iii) Detection of lipid oxidative damage by assaying for the advanced lipid peroxidation end products 4-hydroxynonenal (4-HNE or HNE), malondialdehyde (MDA), 8-iso-prostaglandin F2α and thiobarbituric acid reactive substances (TBARS) (Miller et al., 2012). Mean percentage of change from baseline to visit 2.

End point type	Secondary

End point timeframe:

At week 4

End point values	Simvastatin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	18		
Units: Percentage of change				
arithmetic mean (confidence interval 95%)				
Nos. Lymph events gated	-381.57 (-1151.38 to 388.24)	-280.97 (-958.49 to 396.55)		
Nos. CD3+T cell events gated	196.26 (-1035.94 to 1428.46)	286.48 (-798.13 to 1371.09)		
CD4+ T cells	-113.84 (-238.98 to 11.30)	13.73 (-99.59 to 127.04)		
CD8+ T cells	-344.68 (-615.56 to -73.79)	-209.93 (-463.84 to 43.98)		
B cells	-74.50 (-464.45 to 315.45)	-253.57 (-606.90 to 99.74)		
CD8+ non-T cells	-110.50 (-209.31 to 11.69)	-41.85 (-137.44 to 53.74)		
CD4+ IFN+ (Th1) cells	-37.60 (-672.04 to 596.84)	165.81 (-425.07 to 756.68)		
CD4+ IL17+ (Th17) cells	-138.72 (-313.51 to 36.06)	-71.45 (-240.23 to 97.32)		
8OH	-24.40 (-53.26 to 4.46)	26.69 (-0.40 to 53.77)		
Nitro	59.14 (10.40 to 107.87)	66.60 (25.78 to 107.42)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse event data were collected from June 2019 to 12 October 2022, covering each participant from baseline to one month post-final visit, with individual assessment periods of about 24 weeks depending on enrollment and visit schedule.

Adverse event reporting additional description:

Adverse Event (AE): Any untoward medical occurrence in a trial participant given a medicinal product, not necessarily causally related to treatment.
Serious AE, SAR, or unexpected SAR: An AE or reaction that results in death, is life-threatening, or causes serious health consequences.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	10

Reporting groups

Reporting group title	Simvastatin

Reporting group description:

Simvastatin is part of the pharmacotherapeutic group of HMG-CoA reductase inhibitors (ATC-Code: C10A A01). Simvastatin is licensed within the EU for hypercholesterolemia and cardiovascular prevention but for this trial its use will be outside its licensed indication.
The starting dose at baseline was 40 mg of Simvastatin or placebo (one tablet) to be taken orally in the evening. This was up titrated at Visit 2 (week 4) to 80 mg (two tablets) if all safety parameters were met at Visit 2. Participants were allocated one bottle each containing 220 tablets for the duration of the study. There was therefore one drug dispensation at baseline, and the patient was reminded to up-titrate after one month at Visit 2.

Reporting group title	Placebo

Reporting group description:

Matched placebo taking a dummy pill (Placebo IMP: gelatine tablet with added cellulose microcrystalline).
The starting dose at baseline for placebo was 1 tablet to be taken orally in the evening. This was up titrated at Visit 2 (week 4) to 2 tablets if all safety parameters were met at Visit 2. Participants were allocated one bottle each containing 220 tablets for the duration of the study. There was therefore one drug dispensation at baseline, and the patient was reminded to up-titrate after one month at Visit 2.

Serious adverse events	Simvastatin	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	Simvastatin	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 20 (30.00%)	11 / 20 (55.00%)	
Injury, poisoning and procedural complications			
Bone fracture			
subjects affected / exposed	0 / 20 (0.00%)	2 / 20 (10.00%)	
occurrences (all)	0	2	
Nervous system disorders			
Movement disorder			
subjects affected / exposed	0 / 20 (0.00%)	2 / 20 (10.00%)	
occurrences (all)	0	2	
Numbness			
subjects affected / exposed	0 / 20 (0.00%)	2 / 20 (10.00%)	
occurrences (all)	0	2	
Speech difficulties			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Brain fog			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Flu-syndrome			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Fatigue			
subjects affected / exposed	1 / 20 (5.00%)	1 / 20 (5.00%)	
occurrences (all)	1	1	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Diarrhea			
subjects affected / exposed	1 / 20 (5.00%)	1 / 20 (5.00%)	
occurrences (all)	1	1	
Hepatobiliary disorders			

Increased ALT and/or AST			
subjects affected / exposed	3 / 20 (15.00%)	0 / 20 (0.00%)	
occurrences (all)	3	0	
Endocrine disorders			
Increased TSH			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Muscle pain and stiffness			
subjects affected / exposed	2 / 20 (10.00%)	6 / 20 (30.00%)	
occurrences (all)	3	6	
Back pain			
subjects affected / exposed	0 / 20 (0.00%)	2 / 20 (10.00%)	
occurrences (all)	0	2	
Increased CK			
subjects affected / exposed	1 / 20 (5.00%)	1 / 20 (5.00%)	
occurrences (all)	1	1	
Headache			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	2	
Infections and infestations			
Dental infection			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Urinary tract infection			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
COVID-19			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 January 2018	Additional information and clarifications related to the study procedures have been incorporated into the protocol (Protocol Version 1.2, dated 12 Jan 2018). Accordingly, the following documents have been amended: - Participant Information Leaflet (PIL) Version 1.1, dated 04 Jan 2018; - Consent Form Version 1.1, dated 04 Jan 2018; - Pregnancy Monitoring Form Version 1.1, dated 04 Jan 2018; - Pregnancy Monitoring Consent Form Version 1.1, dated 04 Jan 2018; - IMPD Versions 1.2, 1.3, and 1.4.
26 August 2018	An update to the protocol has been made in response to the REC Provisional Opinion and submitted to the MHRA. The following new documents have been included: - Protocol Version 1.2, dated 12 Jan 2018; - IMPD Version 1.4, dated 01 Feb 2018.
19 December 2018	An update to the protocol has been made to clarify the storage of the Investigational Medicinal Product (IMP) at the site and to remove the PASAT assessment (Protocol Version 1.4). The IMPD has been updated accordingly to Version 1.5. Validated study instruments have also been submitted for REC review and approval.
15 May 2019	This non-substantial amendment updated the protocol to Version 1.5 to provide clarification on the randomisation process at Visit 1.
29 September 2020	The protocol has been updated to Version 1.6 to include primary progressive multiple sclerosis (PPMS) patients. Associated documents, including the Participant Information Sheet (PIS) and Informed Consent Form (ICF), have been updated accordingly. The Reference Safety Information (RSI) has been revised, and two new documents — the Retinal Imaging Questionnaire and COVID-19 Participant Information Leaflet (PIL) — have been added.
26 November 2020	This non-substantial amendment updates the GP Letter template, Neurologist Letter template, Diary Card template, and 24-hour Contact Card to reflect the new trial title following the inclusion of primary progressive multiple sclerosis (PPMS) patients: "A double-blind, randomised, placebo-controlled, single-site study of high-dose simvastatin treatment for progressive multiple sclerosis: impact on vascular perfusion and oxidative damage".
24 October 2022	This amendment includes the removal of the Independent Data Monitoring Committee (IDMC), an amendment to the End of Trial definition, and an update to the imaging (MRI) protocol.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

Recruitment and follow-up were affected by COVID-19, causing delays and out-of-window visits. The small sample size and single-site design may limit generalisability and consistency of results.

Notes: