

Effect of repurposed simvastatin on disability progression in secondary progressive multiple sclerosis (MS-STAT2): a phase 3, randomised, double-blind, placebo-controlled trial



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Summary

Background Despite the success of immune modulation in the treatment of relapsing multiple sclerosis, disability progression is a major problem driven by multiple mechanisms. Comorbidities (eg, vascular risk) and ageing are thought to augment these neurodegenerative pathologies. In the phase 2b MS-STAT trial of simvastatin (80 mg) versus placebo in secondary progressive multiple sclerosis (SPMS), the adjusted difference in brain atrophy rate between groups was -0.254% per year: a 43% reduction. In this phase 3 MS-STAT2 trial, we aimed to assess the efficacy of simvastatin versus placebo in slowing the progression of disability in SPMS.

Methods This phase 3, randomised, double-blind, parallel group, placebo-controlled clinical trial was conducted at 31 neuroscience centres and district general hospitals in the UK. Participants aged 18–65 years with a diagnosis of SPMS and an Expanded Disability Status Scale (EDSS) of between 4.0 and 6.5 were eligible and randomly assigned (1:1) to oral simvastatin (80 mg) or matched placebo for up to 4.5 years, based on a minimisation algorithm within an independent and secure online randomisation service. All participants, site investigators, and the trial coordinating team were masked to treatment allocation. The primary outcome was time to 6-month EDSS confirmed disability progression (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) assessed in all randomly assigned participants (intention-to-treat analysis) without imputation. This study is registered with ClinicalTrials.gov (NCT03387670) and is on the ISRCTN registry (ISRCTN82598726). The study is completed.

Findings Between May 10, 2018, and July 26, 2024, 1079 patients were screened for eligibility and 964 participants were randomly assigned, with 482 (50%) in the placebo group and 482 (50%) in the simvastatin group. Of all 964 participants, 704 (73%) were female and 260 (27%) were male, with a mean age of 54 years (SD 7). 173 (36%) of 482 participants in the placebo group and 192 (40%) of 482 participants in the simvastatin group had 6-month confirmed disability progression (adjusted hazard ratio 1.13 [95% CI 0.91 to 1.39], $p=0.26$). Although no emergent safety issues were seen, there was one serious adverse reaction (rhabdomyolysis) in the simvastatin group. 12 (2%) of 482 participants in the placebo group and five (1%) of 482 participants in the simvastatin group had a cardiovascular serious adverse event.

Interpretation The MS-STAT2 trial did not show a treatment effect of simvastatin in slowing disability progression in SPMS. Simvastatin use in multiple sclerosis should be confined to existing vascular indications.

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Introduction

The therapeutic options for reducing disability progression in progressive multiple sclerosis are limited compared with the wide range of effective immunomodulatory treatments for relapsing multiple sclerosis.¹

Central to this limitation is the inadequate understanding of the underlying dynamic pathobiology that fluctuates over many decades. The relative contribution of mechanisms including active inflammatory infiltrates, chronic compartmentalised inflammation, ion imbalance,

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Research in context

Evidence before this study

When we published the phase 2b MS-STAT trial, we searched for studies in MEDLINE (from Jan 1, 1946), Embase (from Jan 1, 1974), PubMed (from Jan 1, 1996), Cochrane Database of Systematic Reviews (CDSR; from Jan 1, 1995), CENTRAL (from Jan 1, 1996), DARE (from Jan 1, 1994), and the Health Technology Assessment Database (from Jan 1, 1996) to April 8, 2013, using the keywords “multiple sclerosis” AND “statins”. We included trials, observational studies, and laboratory studies in humans and animals. The book of abstracts from the meetings of the European Committee for Treatment and Research in Multiple Sclerosis for the previous 8 years was also searched (2005 to 2012). The resulting papers were examined manually. Seven randomised controlled trials were identified: one in clinically isolated syndrome (n=81), one in optic neuritis (n=64), and five in relapsing-remitting multiple sclerosis, these with statins as a randomised add-on to β -interferon (n=540; 392 assigned simvastatin and 148 assigned atorvastatin). Overall, these studies did not demonstrate a consistent benefit of statins. The phase 2b MS-STAT trial found that simvastatin reduced whole brain atrophy rate in people with secondary progressive multiple sclerosis (SPMS) and had a positive impact on some secondary

and failed remyelination varies across time and between individuals—but culminates in progressive neurodegeneration.^{2,3} This progressive neurodegeneration leads to gradual deterioration in domains such as walking, cognition, vision, and sphincter control, all with high individual and societal health economic costs.

The only two agents widely approved (ocrelizumab and siponimod) for progressive multiple sclerosis are largely restricted to those with evidence of ongoing inflammatory activity.^{4,5} Effectiveness is modest: long-term studies estimate that around 40% of those treated with siponimod had disability worsening at 4 years, and 80% treated with ocrelizumab progressed after a decade.^{6,7}

Separately, epidemiological studies have consistently reported associations between multiple sclerosis disease severity and vascular comorbidities. These are common in progressive multiple sclerosis populations and are associated with reaching important disability milestones around 6 years earlier than participants without vascular comorbidity.^{8,9}

Experimental models of multiple sclerosis have indicated that statins, commonly used for both primary and secondary prevention of vascular disease, could also be useful in ameliorating the pathobiology of multiple sclerosis through mechanisms such as improving vascular perfusion, suppressing astroglial and vascular activation, attenuating oxidative damage, and modulating the neurotoxic secretory phenotype of neural stem cells.^{10–13} These effects are believed to be

disability outcomes. Our search did not identify any other trials of statins in SPMS. We updated this search in MEDLINE, Embase, PubMed, CDSR, CENTRAL, Epistemonikos, ClinicalTrials.gov, and the International Clinical Trials Registry Platform from April 8, 2013, to March 11, 2025. Two further trials in relapsing-remitting multiple sclerosis were identified, both with atorvastatin added to β -interferon (n=249), neither of which showed benefit on the primary outcome. No further trials in SPMS (or other multiple sclerosis classifications) were reported. The searches were not limited to the English language.

Added value of this study

In contrast to the previous phase 2b study, this large phase 3 randomised controlled trial did not show any evidence that simvastatin slows disability progression in SPMS. The study design was robust with appropriate performance characteristics.

Implications of all the available evidence

Combined with the overall absence of efficacy in previous relapsing-remitting cohorts, there is no place for the use of simvastatin (and probably all statins) as a disease-modifying treatment in multiple sclerosis. Statins continue to have a crucial role in primary and secondary vascular protection.

mediated through pleiotropic mechanisms that might be independent of systemic cholesterol lowering, operating predominantly through modification of small GTPase activity.^{14–16}

In the phase 2b, MS-STAT, double-blind trial, 140 participants with secondary progressive multiple sclerosis (SPMS) were randomly assigned (1:1) to simvastatin (80 mg per day) or matched placebo.¹⁷ Over the course of 25 months, the mean annualised whole brain atrophy rate was significantly lower in patients in the simvastatin group (0.288% per year [SD 0.521]) compared with the placebo group (0.584% per year [0.498]).^{18,19} The adjusted difference in atrophy rate between groups was -0.254% per year (95% CI -0.422 to -0.087 ; $p=0.003$); a 43% reduction in annualised rate. There was also a statistically significant difference in favour of simvastatin versus placebo for the Expanded Disability Status Scale (EDSS) and Multiple Sclerosis Impact Scale-29 (MSIS-29) version 2 secondary outcomes, and the simvastatin treatment was well tolerated.¹⁷ In this phase 3 MS-STAT2 trial, we aimed to assess the efficacy of simvastatin versus placebo in slowing the progression of disability in SPMS.

Methods

Study design and participants

We undertook this phase 3, randomised, double-blind, parallel group, placebo-controlled clinical trial of participants with SPMS (with evidence of disability progression in the preceding 2 years), investigating the

effect of oral simvastatin in slowing the progression of the disease. 31 neuroscience centres and district general hospitals in the UK were included. Participants were confirmed to have multiple sclerosis as per McDonald criteria.^{20–24} The major inclusion criteria, similar to the previous MS-STAT trial, were participants aged 25–65 years with EDSS between 4·0 and 6·5 inclusive and a diagnosis of SPMS with evidence of steady disability progression in the preceding 2 years (with either an increase of at least 1 point in the EDSS if <6·0 or 0·5 point if ≥6·0, or a clinically documented increase in disability). Only newly licensed (2017 onwards) disease-modifying treatments for SPMS in the UK were allowable. Participants were ineligible if they had primary progressive multiple sclerosis; had a relapse or had been treated with corticosteroids within 3 months of screening; or used immunosuppressants, disease-modifying treatments within 6 months (apart from those allowed), or monoclonal antibodies within the previous 12 months. They were not allowed to be on statins already, have type 1 diabetes, or have been started on fampridine within the previous 6 months. Participant sex and ethnicity (according to UK Office for National Statistics groups) were self-reported. This Article refers to the current protocol (version 8; Feb 26, 2024; appendix pp 2–86). The appendix (pp 73–79) lists the protocol amendments with reasons. Further details on the protocol, eligibility criteria, and study design are available.²⁵

The study was conducted in accordance with the Declaration of Helsinki and International Council for Harmonisation Good Clinical Practice guidelines. The National Research Ethics Service Committee (London, Westminster) reviewed the trial protocol and materials to be given to participants (approved Oct 9, 2017; 17/LO/1509). All participants provided written informed consent before entering the study. This study is registered with ClinicalTrials.gov (NCT03387670) and is on the ISRCTN registry (ISRCTN82598726). The trial is completed.

Randomisation and masking

Participants were randomly assigned (1:1) to either simvastatin or placebo using an online service with a minimisation algorithm incorporating a random element. There was a 40% chance of simple random allocation between groups and 60% chance of being assigned to the group that would best maintain the balance of the minimisation factors, which ensured an overall probability of 80% of randomisation into the group that would best balance the minimisation factors. The minimisation factors were site, sex (male or female), baseline EDSS (4·0–5·5 or 6·0–6·5), age (<45 or ≥45 years), and use of newly licensed disease-modifying treatments for SPMS (yes or no). Participants and investigators, including pharmacy, treating, and independent assessing neurologists, were masked to treatment allocation. To maintain masking, the online

randomisation system issued a five-digit code to identify the concealed bottles of treatment (capsules 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. The success of masking was not assessed.

Procedures

Participants received either oral 80 mg simvastatin (initially 40 mg at randomisation, then escalated after 1 month if tolerated), or the same quantity of oral placebo taken once daily at night. Participants continued their allocated treatment for between 3 years and 4·5 years. Dose modification could occur as per the protocol.²⁵ Those who had not had confirmed disability progression, as measured by EDSS, by the 3-year timepoint were offered a further extension period of follow-up if they were at a participating site (21 of 31 sites) and there was sufficient time remaining before the end of the trial in 2024. Participants who consented to continue for the extension period remained on their masked intervention for up to another 1·5 years (ie, up to 4·5 years), depending on the time remaining before the end of trial in 2024. Participants who discontinued treatment continued follow-up unless they withdrew consent from participation in the trial. After baseline, participants were seen in clinic at months 1, 3 (telephone only), 6, 12, 18, 24, 30, and 36 with three additional visits at months 42, 48, and 54 for those in the extension. Safety monitoring was performed at each visit. Details of the assessments and safety monitoring conducted at each visit are outlined in the protocol (appendix pp 45–47).

Outcomes

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 the next visit at least 6 months later. The time of confirmed progression was defined as when the initial disability progression occurred. If the increase in EDSS was not confirmed (either because the EDSS had returned to a lower value at the subsequent visit, or because no further follow-up EDSS data were obtained), then this did not contribute as an event for the primary outcome. Participants who died due to multiple sclerosis were considered to have confirmed progression. EDSS scoring was carried out by a masked assessor who followed Neurostatus scoring guidance (version 04/10.2).

Clinical secondary endpoints were: progression by 3 years on a multicomponent measure of disability progression (and subsequently confirmed) comprising one or more of EDSS, timed 25-foot walk (T25FW), or the 9-hole peg test (9HPT), with T25FW and 9HPT

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See Online for appendix

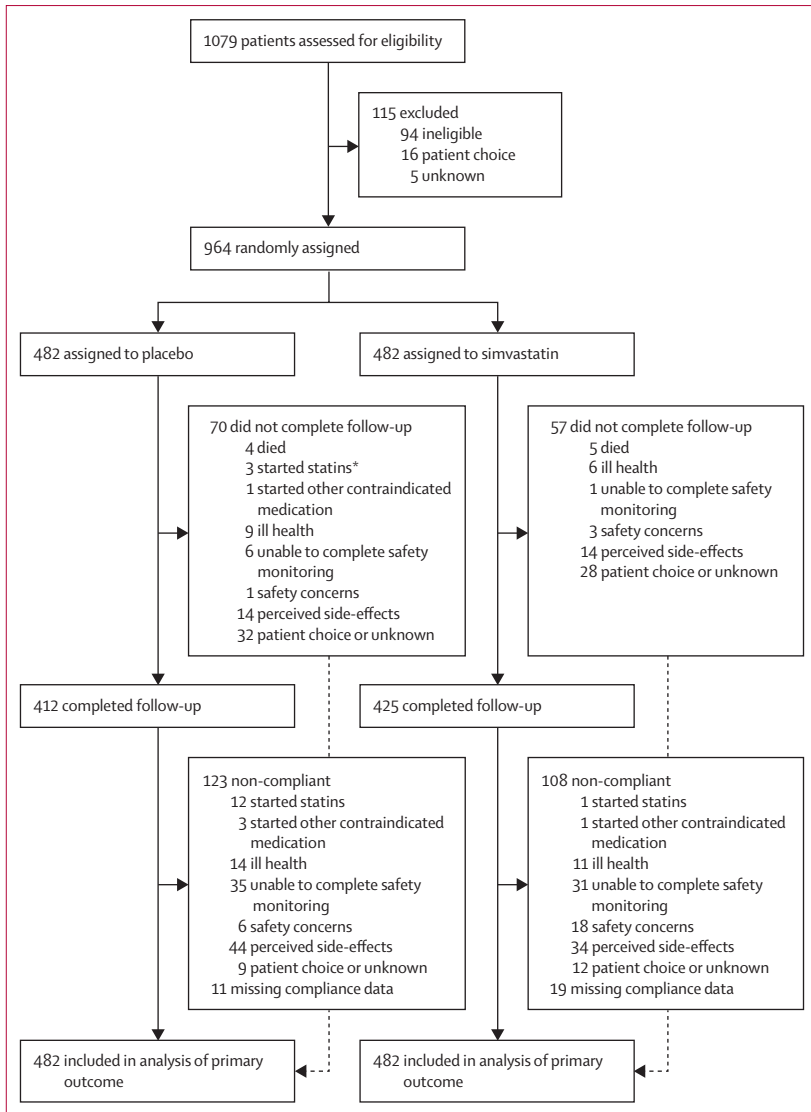


Figure 1: Trial profile
Compliance assessed over the first 3 years of follow-up, or until date of confirmed progression, death, or withdrawal if these happened before 3 years. *Of the three participants who withdrew from the placebo group due to starting statins, one participant was also counted as non-compliant as they had already discontinued the trial medication.

progression defined as at least 20% worsening from baseline (appendix p 134); relapse assessment (number and severity); modified Multiple Sclerosis Functional Composite (MSFC) Z score comprising the T25FW, 9HPT, and Symbol Digit Modalities Test (SDMT); MSFC individual components; Sloan low contrast visual acuity (SLCVA) at contrast 100%, 2.5%, and 1.25%; modified Rankin Scale (mRS); Brief International Cognitive Assessment For Multiple Sclerosis (BICAMS) comprising SDMT, California Verbal Learning Test-II (CVLT-II), and Brief Visuospatial Memory Test-Revised (BVMT-R). Patient-reported secondary endpoints were: MSIS-29v2; Multiple Sclerosis Walking Scale-12

version 2 (MSWS-12v2); Modified Fatigue Impact Scale 21 (MFIS-21); and Chalder Fatigue Questionnaire (CFQ).

The EDSS, T25FW, and 9HPT were measured at baseline and at 6-monthly intervals to 4.5 years; the SDMT, SLCVA, mRS, MSIS-29v2, MSWS-12v2, MFIS-21 and CFQ yearly up to 3 years; and the CVLT-II and BVMT-R at baseline and 3 years. Participants attended in person for the follow-up visits if possible. If participants were unable to attend (eg, due to COVID-19 restrictions), a telephone EDSS assessment was done, and patient-reported outcomes were collected remotely (appendix p 49).²⁶ At each visit, or when contacted by participants at any point during the trial, adverse events were recorded and classified based upon International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Good Clinical Practice principles. The severity of adverse events was assessed by treating clinicians according to National Institutes of Health Common Terminology Criteria for Adverse Events version 5, and potential causality in relation to trial medication was assessed. The appendix (pp 60–66) has further details of adverse event reporting.

Statistical analysis

To have 90% statistical power to show a 30% relative reduction in disability progression for simvastatin versus placebo, at the conventional 5% significance level, the trial required 330 confirmed progression events. To observe this number of events the sample size was originally set to 1180 patients (590 patients per group) with fixed follow-up of 3 years. In February, 2021, the follow-up was extended to up to 4.5 years. As a result, the sample size was revised to 1050 participants (525 per group) because of the associated increase in the expected proportions of patients with confirmed progression. The final sample size assumed that by 4.5 years the placebo progression rate would be 49% and there would be up to 32% loss to follow-up (appendix pp 99–100).²⁵

The primary analysis included all participants who were randomly assigned, irrespective of subsequent compliance with allocated treatment (ie, including all participants whether or not they took the prescribed study medication). 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.

The primary endpoint, confirmed disability progression on EDSS, was compared between the simvastatin and placebo treatment groups up to 4.5 years using a Cox proportional hazards model. The estimated hazard ratio (HR) along with its 95% 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). Only one participant was on a newly licensed (since 2017) disease-modifying treatment at the time of randomisation,

so this minimisation factor was not adjusted for in any analysis. Kaplan–Meier curves were produced to show the cumulative probability of confirmed progression over time since randomisation in each group. Participants who died due to non-multiple sclerosis causes or withdrew from the study for any reason were censored at the last visit at which progression could have occurred, which would be their penultimate study visit, as there was the need to confirm the progression event. The proportional hazards assumption was assessed using a log–log plot of survival in the two treatment groups.

A prespecified subgroup analysis was conducted to examine whether the COVID-19 pandemic had any influence by splitting the follow-up into three periods: before the start of COVID-19-related public health restrictions (before March 16, 2020); when public health restrictions were present (from March 16, 2020, to July 19, 2021); and after the end of COVID-19-related public health restrictions in the UK (after July 19, 2021). Kaplan–Meier plots were produced for each period by treatment group, and a Cox proportional hazards model was fitted, including period and an interaction between period and treatment group. Three prespecified sensitivity analyses on the primary outcome were conducted to estimate the treatment effect: first, including both confirmed progression and unconfirmed progression, in which the participant ended follow-up before the event could be confirmed (ie, it was not known whether the initial progression event was confirmed or not); second, including only visits with the least effect of COVID-19-related public health restrictions; and finally, including only patients who were compliant with their randomly assigned intervention (appendix pp 110–15).

A mixed-effects logistic regression model was used to compare the groups at 3 years on confirmed disability progression on the multicomponent measure of disability and its components, and disability progression on the mRS (defined as any increase between baseline and 3 years). 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.

A constrained longitudinal data analysis approach was used to compare the continuous outcome measures between the treatment groups at each follow-up visit, with the endpoint of interest being the difference at 3 years.²⁷ As is standard, the model included an interaction between visit and treatment group to allow estimation of the mean difference in score at each visit with the treatment effects at baseline constrained to be zero. An unstructured covariance matrix for the residuals was used to allow for correlation between repeated measures. The minimisation variables (ie, sex, age, and baseline EDSS) and their interactions with visit were included as fixed effects. A random effect for study site was included

	Placebo (n=482)	Simvastatin (n=482)
Age (years)	54.4 (6.8)	54.2 (6.8)
Sex		
Female	351 (73%)	353 (73%)
Male	131 (27%)	129 (27%)
Ethnic origin		
White	466 (97%)	463 (96%)
Asian or Asian British	9 (2%)	12 (2%)
Black or Black British	3 (1%)	1 (<1%)
Mixed	3 (1%)	6 (1%)
Unknown	1 (<1%)	0
Multiple sclerosis duration (years)	23.4 (9.3)	22.3 (9.4)
Secondary progressive multiple sclerosis duration (years)	7.2 (5.0)	7.0 (4.7)
Relapse in past 12 months	24 (5%)	25 (5%)
Total cholesterol (mmol/L)	5.4 (1.1), n=478	5.4 (1.1), n=479
Expanded Disability Status Scale step score		
4–5.5	135 (28%)	140 (29%)
6	177 (37%)	177 (37%)
6.5	170 (35%)	165 (34%)
Timed 25-foot walk speed (feet per s)	2.2 (1.2), n=476	2.2 (1.2), n=477
9-hole peg test speed (s ⁻¹ × 100)	3.4 (1.0)	3.3 (1.0)
Symbol Digit Modalities Test Z score ≤-1.5	253/470 (54%)	270/474 (57%)
California Verbal Learning Test-II Z score ≤-1.5	176/470 (37%)	171/473 (36%)
Brief Visuospatial Memory Test-Revised Z score ≤-1.5	57/458 (12%)	55/470 (12%)
SLCVA 100% contrast (out of 60)	51.1 (10.4), n=468	51.3 (10.1), n=472
SLCVA 2.5% contrast (out of 60)	25.9 (13.2), n=465	26.3 (13.0), n=463
SLCVA 1.25% contrast (out of 60)	13.7 (12.2), n=457	13.7 (12.1), n=458
MSIS-29 version 2 physical (out of 100)	54.6 (19.2), n=458	54.3 (19.4), n=469
MSIS-29 version 2 psychological (out of 100)	40.2 (22.5), n=476	38.4 (21.6), n=477
Multiple Sclerosis Walking Scale-12 version 2 (out of 100)	66.7 (18.4), n=455	67.9 (18.0), n=458
Modified Fatigue Impact Scale 21 (out of 100)	57.0 (19.5), n=440	57.5 (19.2), n=444
Chalder Fatigue Questionnaire (out of 100)	52.3 (19.0), n=477	52.8 (18.6), n=475
On siponimod treatment	0	1 (<1%)

Data are mean (SD), n (%), or n/N (%). Patient numbers are shown if group size was less than 482. SLCVA=Sloan low contrast visual acuity. MSIS=Multiple Sclerosis Impact Scale.

Table 1: Baseline characteristics of the intention-to-treat population

for each visit. For MSFC composite Z score, T25FW, 9HPT, SLCVA, SDMT, CVLT-II, and BVMT-R, the mixed model included the values at baseline and 3 years. For MSIS-29v2, MSWSv2, MFIS-21, and CFQ, the mixed model included the values at baseline and years 1, 2, and 3.

Plots of the residuals from the model for MSFC Z score, MSWSv2, and SLCVA at all three contrast levels showed marked departures from normality. Therefore, bias corrected and accelerated bootstrap 95% CIs based on 2000 replications were used for inference. Bootstrap samples were taken with clustering on individual and were stratified by study site and treatment group. Prespecified COVID-19 subgroup and sensitivity analyses were conducted for relapse rate, MSIS-29v2, MSWSv2, MFIS-21, and CFQ (appendix pp 122–27).

A formal interim analysis was conducted on an annual basis to present safety data and the treatment effect on the

	Placebo	Simvastatin	Hazard ratio (95% CI)	Odds ratio (95% CI)	p value
Primary analysis, confirmed disability progression on EDSS	173/482 (36%)	192/482 (40%)	1.13 (0.91–1.39)	..	0.26
Sensitivity analysis, unconfirmed events	210/482 (44%)	227/482 (47%)	1.10 (0.91–1.33)	..	0.32
Sensitivity analysis, COVID-19*	98/300 (33%)	105/315 (33%)	..	1.03 (0.73–1.45)	0.85
Per-protocol analysis, high dose	125/316 (40%)	139/330 (42%)	1.12 (0.87–1.43)	..	0.38
Per-protocol analysis, high or low dose	129/331 (39%)	145/350 (41%)	1.12 (0.88–1.42)	..	0.37

Data are n/N (%), unless otherwise specified. Sensitivity analysis for unconfirmed events includes both confirmed progression and unconfirmed progression, in which the participant ended follow-up before the event could be confirmed (ie, not known whether initial progression event was confirmed or not). Sensitivity analysis for COVID-19 examined unconfirmed EDSS progression between baseline and the 3-year visit in participants who had EDSS assessed at an in-person baseline visit before March 16, 2020, and at an in-person 3-year visit after July 19, 2021 (ie, during time periods when COVID-19 related public health restrictions were not in force; appendix pp 110–13). EDSS=Expanded Disability Status Scale. *Odds ratio and its 95% CI are given for this analysis.

Table 2: Effect of simvastatin treatment on the primary outcome, confirmed disability progression on EDSS, and sensitivity and per-protocol analyses

primary outcome to an independent data monitoring committee. A Haybittle–Peto stopping boundary of $p < 0.001$ was considered for efficacy, which preserved the $p < 0.05$ level for statistical significance in the final analysis. There was no formal interim futility analysis. Data analysis was performed with Stata version 18.5. The statistical analysis plan is available in the appendix (pp 89–128).

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, or data interpretation. The UK Multiple Sclerosis Society was involved in reviewing the manuscript.

Results

Between May 10, 2018, and Sept 29, 2021, 1079 patients were assessed for eligibility and 964 participants were randomly assigned, with 482 (50%) assigned to the placebo group and 482 (50%) assigned to the simvastatin group (figure 1). There were 612 participants whose final planned follow-up visit was at 3 years and 352 participants who were entered into the extension to attend further visits up to 4.5 years (appendix p 138). Median participant duration in the trial was therefore 3 years (IQR 3–4.5 years). 127 participants (13%) left the trial before they had completed their final intended visit: nine who died, 19 for medical reasons (ill health or contraindicated medications), 11 due to safety concerns (including if unable to complete safety monitoring), 28 due to perceived side-effects, and 60 due to patient choice or unknown (figure 1). The proportion of patients compliant with their randomised intervention before censoring in the primary analysis was similar in the two treatment groups: 348 (74%) of 471 patients in the placebo group and 355 (77%) of 463 patients in the simvastatin group (appendix p 140). The most common reasons for non-compliance were perceived side-effects (44 participants in the placebo group, 34 in the simvastatin group) and that safety monitoring could not be completed (35 placebo, 31 simvastatin). Participants stopping trial medication due to a gap in safety monitoring was largely due to difficulties in obtaining the necessary safety blood tests for the period when COVID-19-related public health restrictions were in force.

Table 1 gives the baseline characteristics of the participants included in the primary analysis. Of the 964 participants, 704 (73%) were female and 260 (27%) were male. There was a low pre-trial relapse rate of 5% in the previous year. The two treatment groups had no imbalances of concern in baseline characteristics. Only one patient was on disease-modifying treatment (siponimod) coming into trial.

There was no material difference between the simvastatin and the placebo groups for the primary endpoint, confirmed disability progression on EDSS (table 2 and figure 2). 365 (38%) of all 964 participants had confirmed progression up to 4.5 years of follow-up: 173 (36%) of 482 participants in the placebo group and 192 (40%) of 482 participants in the simvastatin group.

From the Cox proportional hazards model adjusted for sex, age, and baseline EDSS and stratified by study site, the difference in hazard of confirmed progression was not statistically significant and the 95% CI was sufficiently narrow to exclude a clinically meaningful benefit (adjusted HR 1.13 [95% CI 0.91–1.39]; $p = 0.26$). No material departures were noted from the proportional hazards assumption. Results of sensitivity analyses and the per-protocol analysis were similar to those for the primary analysis and did not show evidence for a difference in disability progression on EDSS between groups (table 2).

There was also no evidence for a benefit of simvastatin over placebo on any of the secondary endpoints (table 3). On the multicomponent measure of disability, the numbers with confirmed progression by 3 years were 242 (55%) of 442 patients in the placebo group and 261 (59%) of 446 patients in the simvastatin group (adjusted odds ratio [OR] 1.17 [95% CI 0.89 to 1.53]; $p = 0.26$). There was no statistically significant difference between groups on the EDSS or T25FW components when analysed separately. However, there was evidence of a difference on the 9HPT component, with confirmed progression in fewer participants on placebo (32 [7%] of 442 participants) compared with simvastatin (51 [11%] of 446 participants; adjusted OR 1.68 [95% CI 1.05 to 2.69]; $p = 0.031$), but interpretation here should be cautious in view of the number of secondary

analyses carried out and the fact that the p value is only slightly below the significance threshold. Furthermore, there was little difference in the mean 9HPT speed at 3 years ($0.03 \text{ s}^{-1} \times 100$ faster in the simvastatin group [95% CI -0.05 to 0.12]; $p=0.48$; table 3). The MSFC Z score and T25FW speed at 3 years were similar between groups. Visual performance at 3 years was similar for simvastatin and placebo, with the mean score for SLCVA being similar for the two groups at all three contrast percentages. There was no material difference between the simvastatin group and the placebo group on the mRS with disability progression at 3 years in 148 (38%) of 393 participants in the placebo group and 165 (40%) of 413 participants in the simvastatin group (adjusted OR 1.10 [95% CI 0.82 to 1.47]; $p=0.53$). There was no evidence for a treatment effect on cognition. The simvastatin group and the placebo group had similar mean scores at 3 years for each of the cognitive tests that make up BICAMS: SDMT, CVLT-II, and BVMT-R (table 3).

There was no significant difference between the simvastatin group and the placebo group on any of the patient-reported outcomes (table 3). There was some evidence that the relapse rate was higher in the simvastatin group than in the placebo group (table 3), although numerically the incidence rate per person-year was low: 0.05 in the placebo group and 0.07 in the simvastatin group.

The COVID-19 subgroup analysis found no evidence of a difference in treatment effect on the primary outcome between the periods before, during, or after COVID-19 public health restrictions were in place ($p=0.22$ from test of interaction between period and treatment; appendix p 144). However, there was strong evidence ($p<0.0001$) that the hazard of disability progression was greater when COVID-19 public health restrictions were present, compared to when they were absent, as can be seen in the Kaplan–Meier plots (appendix p 141). Patient-reported outcomes were similar in the COVID-19 sensitivity analysis. COVID-19 subgroup analysis of the patient-reported outcomes and relapse rate found no evidence of a difference of effect of treatment by period (appendix pp 145–48).

79 participants initiated disease-modifying treatments during follow-up (43 [9%] of 482 participants in the simvastatin group; 36 [7%] of 482 participants in the placebo group). Of 79 participants, 73 were started on siponimod.

Starting a statin was the primary cause for 15 (2%) of 964 participants to withdraw from the trial or to discontinue trial medication: 14 (3%) of 482 participants in the placebo group and one (<1%) of 482 participants in the simvastatin group. Of the three participants who withdrew from the placebo group due to starting statins, one participant was also counted as non-compliant as they had already discontinued the trial medication. Data on other concomitant treatments and the prevalence of

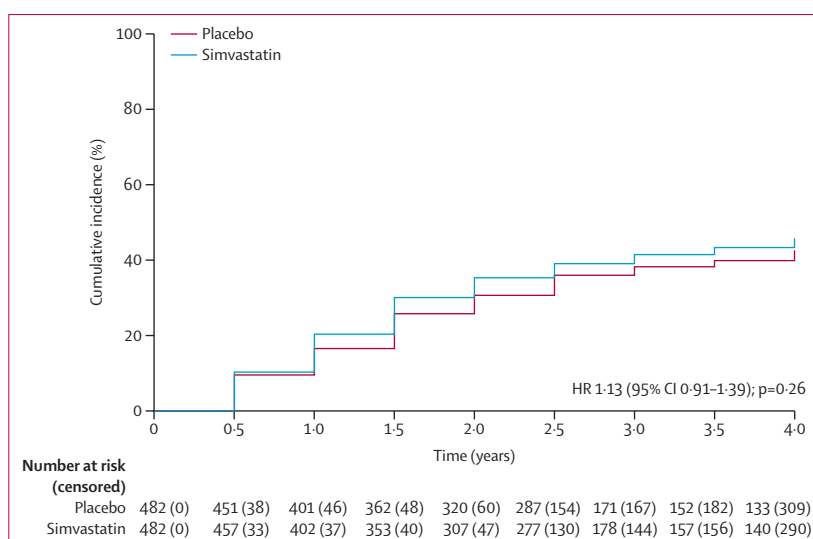


Figure 2: Kaplan–Meier estimate of cumulative proportion with confirmed EDSS progression in each treatment group

EDSS=Expanded Disability Status Scale. HR=hazard ratio.

comorbidities in each group are shown in the appendix (pp 142–43).

No emergent safety issues or suspected unexpected serious adverse reactions were reported. There was one serious adverse reaction: a patient in the simvastatin group was admitted to hospital for rhabdomyolysis, which began 56 days after starting treatment and resolved without sequelae. Table 4 summarises the safety data by treatment group. 12 (2%) of 482 participants in the placebo group had a cardiovascular serious adverse event, compared with five (1%) of 482 participants in the simvastatin group (appendix pp 150–53). A health economic analysis will be reported later.

Discussion

In this double-blind, randomised, placebo-controlled, phase 3 trial in participants with progressing SPMS, we found no advantage of simvastatin 80 mg once per day compared with placebo on any measure of multiple sclerosis progression. This result is in contrast with the phase 2b MS-STAT trial in which a significant reduction in whole brain atrophy and some benefits on clinical endpoints were seen.¹⁷

The trial was carried out successfully, despite going through the COVID-19 pandemic. The rate of disability progression was in line with expectations, with EDSS confirmed disability progression alone at around 40% up to 4.5 years, and the multicomponent measure of progression approaching 60% at 3 years. The demographics of the population were typical, with a mean age of 54 years (SD 7) and duration of progression of 7 years (5). There was good adherence to trial medication, and a low proportion of participants did not complete follow-up (13%). Despite the high dose of simvastatin, the safety profile was good and only one case of rhabdomyolysis

	Placebo	Simvastatin	Adjusted odds ratio (95% CI)	Adjusted mean difference (95% CI)	Adjusted incidence rate ratio (95% CI)	p value
Multicomponent disability progression	242/442 (55%)	261/446 (59%)	1.17 (0.89 to 1.53)	0.26
Expanded Disability Status Scale	150/442 (34%)	166/446 (37%)	1.15 (0.87 to 1.52)	0.34
T25FW	145/442 (33%)	158/446 (35%)	1.14 (0.85 to 1.52)	0.39
9HPT	32/442 (7%)	51/446 (11%)	1.68 (1.05 to 2.69)	0.031
Modified Rankin Scale	148/393 (38%)	165/413 (40%)	1.10 (0.82 to 1.47)	0.53
MSFC						
Z score	-0.3 (1.2), n=383	-0.3 (1.2), n=402	..	0.02 (-0.09 to 0.14)	..	*
T25FW (feet per s)	1.9 (1.3), n=373	1.9 (1.2), n=389	..	-0.01 (-0.12 to 0.10)	..	0.88
9HPT (s ⁻¹ × 100)	3.3 (1.1), n=383	3.3 (1.1), n=401	..	0.03 (-0.05 to 0.12)	..	0.48
Symbol Digit Modalities Test score (out of 110)	43.8 (13.7), n=377	43.3 (13.9), n=397	..	-0.10 (-1.25 to 1.06)	..	0.87
SLCVA (out of 60)						
100% contrast	50.0 (10.7), n=369	50.5 (9.5), n=389	..	0.08 (-1.01 to 1.16)	..	*
2.5% contrast	24.5 (12.2), n=366	25.6 (12.6), n=388	..	0.59 (-0.79 to 1.81)	..	*
1.25% contrast	12.8 (11.1), n=362	12.7 (11.8), n=376	..	-0.49 (-1.80 to 0.76)	..	*
Brief International Cognitive Assessment for Multiple Sclerosis						
California Verbal Learning Test-II score (out of 80)	47.0 (13.3), n=378	46.8 (13.0), n=399	..	-0.04 (-1.32 to 1.24)	..	0.95
Brief Visuospatial Memory Test-Revised score (out of 36)	20.3 (9.3), n=366	20.2 (8.7), n=386	..	0.27 (-0.67 to 1.22)	..	0.57
Multiple Sclerosis Impact Scale-29 version 2 (out of 100)						
Total score	50.5 (20.4), n=387	51.1 (19.7), n=397	..	1.57 (-0.55 to 3.68)	..	0.15
Physical score	55.3 (21.3), n=389	56.8 (21.2), n=401	..	1.97 (-0.28 to 4.22)	..	0.085
Psychological score	39.8 (23.8), n=405	39.1 (22.8), n=411	..	0.88 (-1.57 to 3.32)	..	0.48
MSWS version 2 (out of 100)	69.0 (20.9), n=386	68.3 (21.0), n=394	..	-1.38 (-3.61 to 0.74)	..	*
Modified Fatigue Impact Scale 21 (out of 100)	54.7 (21.7), n=377	56.2 (20.9), n=391	..	0.96 (-1.31 to 3.23)	..	0.41
Chalder Fatigue Questionnaire (out of 100)	49.0 (18.1), n=398	50.4 (18.2), n=403	..	1.22 (-1.04 to 3.48)	..	0.29
Relapse rate per person-year	68/1348 (0.05), n=482	98/1362 (0.07), n=482	1.43 (1.01 to 2.01)	0.044

Data are n/N (%), mean (SD), or number of relapses/person-years (incidence rate per person-year), unless otherwise stated. Patient numbers are shown if group size was less than 482. Adjusted mean difference is shown for simvastatin relative to placebo. For the following outcomes a positive mean difference favours simvastatin: MSFC, SLCVA, and Brief International Cognitive Assessment for Multiple Sclerosis. For the following outcomes a negative mean difference favours simvastatin: Multiple Sclerosis Impact Scale-29 version 2, MSWS version 2, Modified Fatigue Impact Scale 21, Chalder Fatigue Questionnaire. T25FW=timed 25 foot walk. 9HPT=9-hole peg test. MSFC=Multiple Sclerosis Functional Composite. SLCVA=Sloan Low Contrast Visual Acuity. MSWS=Multiple Sclerosis Walking Scale 12. *Plots of the residuals from the model for MSFC Z score, SLCVA at all three contrast percentages, and MSWS version 2 showed marked departures from normality. Therefore, bias corrected and accelerated bootstrap 95% CIs based on 2000 replications were used for inference. p values are therefore not generated for these models, but can be inferred from the 95% CIs.

Table 3: Effect of simvastatin treatment on the secondary outcomes

was seen (with rapid recovery on stopping treatment). However, despite robust trial operational characteristics and the positive outcome of the phase 2b trial, there was no effect on slowing confirmed progression.

Reviews indicate that around 60% of phase 3 trials result in a successful new treatment, and those within neurology rank among the lowest at around 50%.²⁸ Here, we discuss aspects of the trial cohort, and critically reflect upon the underlying preclinical evidence and phase 2 biomarker selection that led to the conception of MS-STAT2, to examine the discordance of the results between the phase 2 and phase 3 trials.

The MS-STAT2 cohort was broadly similar to the original MS-STAT trial, with similar levels of disability (median EDSS 6.0) and duration of progression (7 years), although mean age was 3 years older in MS-STAT2 compared with MS-STAT (54 years vs 51 years). There was also less relapse activity: the proportion with a relapse in the 12 months before randomisation was 5% in MS-STAT2 compared with 14% in MS-STAT, and the in-trial relapse rate was 0.06 in MS-STAT2 compared with 0.18 in MS-STAT.

From the MS-STAT trial we hypothesised that the dominant potential mechanism of action of simvastatin in SPMS was unlikely to be mediated via peripheral immunomodulation, due to the absence of a treatment effect on a panel of immunological biomarkers and serum neurofilaments concentrations.^{17,29} Moreover, no consistent effect on reducing relapse rate with statins had been seen in relapsing multiple sclerosis trials. Therefore, the aim of the MS-STAT2 trial was to recruit a typical non-relapsing but progressing SPMS population, as this was the population in which we thought a benefit was most likely to be seen. For comparison, a large contemporary real-world observational study of patients with SPMS in the UK has also reported a low annualised relapse rate of 0.01, which supports the contention that the participants recruited into the MS-STAT2 trial were representative of the wider UK SPMS population—an important consideration regarding the external validity of our findings.³⁰

Although an association between vascular comorbidity and more severe current or future disability has been

	Placebo (n=482)					Simvastatin (n=482)				
	Serious adverse events	Notifiable adverse events	Adverse events (non-serious)	Serious adverse reactions	Adverse reactions (non-serious)	Serious adverse events	Notifiable adverse events	Adverse events (non-serious)	Serious adverse reactions	Adverse reactions (non-serious)
Total events (events per 100 participants)	176 (36.5)	9 (1.9)	1868 (387.6)	0 (0.0)	157 (32.6)	158 (32.8)	13 (2.7)	1965 (407.7)	1 (0.2)	167 (34.6)
Participants with one or more event	112 (23%)	8 (2%)	412 (85%)	0	100 (21%)	114 (24%)	12 (2%)	420 (87%)	1 (<1%)	97 (20%)
One event	79 (16%)	7 (1%)	65 (13%)	0	63 (13%)	80 (17%)	11 (2%)	60 (12%)	1 (<1%)	56 (12%)
Two events	18 (4%)	1 (<1%)	79 (16%)	0	23 (5%)	25 (5%)	1 (<1%)	66 (14%)	0	23 (5%)
Three events	8 (2%)	0	68 (14%)	0	9 (2%)	8 (2%)	0	75 (16%)	0	9 (2%)
Four events	3 (1%)	0	43 (9%)	0	4 (1%)	1 (<1%)	0	59 (12%)	0	7 (1%)
Five events	1 (<1%)	0	32 (7%)	0	1 (<1%)	0	0	36 (7%)	0	2 (<1%)
Six events	1 (<1%)	0	41 (9%)	0	0	0	0	29 (6%)	0	0
Seven events	2 (<1%)	0	19 (4%)	0	0	0	0	20 (4%)	0	0
Eight events	0	0	18 (4%)	0	0	0	0	25 (5%)	0	0
Nine events	0	0	14 (3%)	0	0	0	0	11 (2%)	0	0
Ten events	0	0	6 (1%)	0	0	0	0	15 (3%)	0	0
11 events	0	0	6 (1%)	0	0	0	0	4 (1%)	0	0
12 events	0	0	5 (1%)	0	0	0	0	3 (1%)	0	0
13 events	0	0	3 (1%)	0	0	0	0	2 (<1%)	0	0
14 events	0	0	3 (1%)	0	0	0	0	2 (<1%)	0	0
15 or more events	0	0	10 (2%)	0	0	0	0	13 (3%)	0	0

Data are n (n per 100 participants) or n (%).

Table 4: Adverse events by treatment group

consistently shown in multiple cohorts, the vascular profile of MS-STAT2 might be lower than the wider SPMS population. In accordance with Declaration of Helsinki principles, participants were ineligible for MS-STAT2 if, at the investigators' discretion, they were deemed to be at high risk of a vascular event. Proceeding to randomisation, potentially to placebo, when standard of care would include vascular risk modification with a statin was considered unethical for these participants. For comparison, in the MS-SMART trial in SPMS (recruitment 2015–16), around 15% of participants were on statins at trial entry, and vascular comorbidities appear less prevalent in MS-STAT2 (appendix pp 142–43) compared with those found in a meta-analysis of previous trial cohorts.^{31,32} If the mechanism of action of simvastatin in SPMS is mediated via modulation of vascular risk, this might therefore lead to the MS-STAT2 trial underestimating the treatment effect, due to the exclusion of participants with high vascular risk.

The median participant duration in the trial was 3 years (IQR 3–4.5 years), which could simply be too short to see an effect on disability progression based on modulation of vascular risk. Moreover, in standard clinical practice, vascular comorbidity is often treated with a combination of different treatments and perhaps monotherapy with simvastatin might not sufficiently modify vascular risk to improve multiple sclerosis outcomes. A longer (eg, a decade) randomised controlled trial (RCT) of combination therapy targeting vascular risk would be

difficult to carry out. A different way to explore this would be with registry-based approaches, although long-term adherence to medication might be difficult (but not impossible) to establish.

The phase 2 MS-STAT trial sought to test earlier positive experimental evidence suggesting that statins modulate immune responses and confer vascular and neuronal protection.^{11,15,33–36} These preclinical models therefore provided compelling evidence that statins mediated pleiotropic effects upon key pathogenic mechanisms thought to be relevant in SPMS, but this has not translated into human studies.

Of these mechanisms, those supporting immune-mediated actions of statins (inhibition of leukocyte entry into the CNS and attenuation of T-cell proliferation) in inflammatory animal models are more applicable to relapsing multiple sclerosis than SPMS. The neutral results of MS-STAT2 in an SPMS cohort therefore largely represent a failure of the additional non-immunomodulatory (vasculoprotective and neuroprotective) pathways to translate from animal to human studies. A 2024 meta-analysis of the preclinical data supporting both approved and unsuccessful disease-modifying treatment in multiple sclerosis did not identify any aspects of the preclinical studies that predicted whether a disease-modifying treatment was likely to be effective in humans.³⁷ Fundamental to this translational issue is our limited understanding of the key pathological drivers of SPMS, which impedes our ability to create relevant animal models

and hence contributes to neutral trial outcomes. Additionally, the timing of intervention might be important—given that preclinical studies involve treatment soon after or even before disease induction, while the MS-STAT2 trial tested an intervention 20 years or more after disease onset.

The inability to translate a neuroprotective effect of statins from preclinical and observational studies to clinical application is becoming common in neurological conditions, as has also been shown in Parkinson's disease and Alzheimer's disease.^{38,39} Preclinical studies in both progressive multiple sclerosis and other neurodegenerative diseases have highlighted important roles for cholesterol metabolites in glial signalling and remyelination, suggesting more specific targeting of cholesterol pathways within the CNS might be required.^{40–42} Beyond statins, similar attempts to repurpose peripherally active modulators of metabolism to treat central neurodegenerative diseases are underway with GLP-1 receptor agonists—although with disappointing results from a 2025 phase 3 trial in Parkinson's disease.⁴³

Measurement of whole brain atrophy is considered an important biomarker of multiple sclerosis progressive biology.^{18,19} Meta-analyses of RCTs in both relapsing and progressive multiple sclerosis have shown consistent associations between the magnitude of the treatment effect on brain atrophy and the magnitude of the treatment effect upon disability progression.^{44,45} Indeed, for the two licensed treatments for progressive multiple sclerosis, benefits on brain atrophy were seen.^{46,47} However, these results do not necessarily mean that brain atrophy and disability progression are fully congruent. A post-hoc analysis of the original MS-STAT phase 2 trial data found that the effect of simvastatin on brain atrophy significantly mediated 31% of the treatment effect upon EDSS progression.¹⁴ SPMS is a heterogeneous disease, and aspects such as neuronal connectivity and spinal cord atrophy might result in disability worsening in some patients in the absence of brain atrophy or vice versa.⁴⁸

Discordant treatment effects on brain atrophy and disability were seen in 2024 with the successful HERCULES trial of tolebrutinib in non-active SPMS, which showed a reduction in clinical progression (HR 0.69 [95% CI 0.55–0.88]; $p=0.003$) without a significant effect on whole brain atrophy.⁴⁹ The atrophy rate in the placebo group of HERCULES was, however, low, and similar to what has been reported among individuals without multiple sclerosis of a similar age.^{49,50} This low atrophy rate might have constrained the ability of the HERCULES trial to detect a treatment effect on brain volumes. A subcohort of the MS-STAT2 trial will report MRI outcomes in due course, which could improve our understanding of why the positive phase 2 MS-STAT results have not been followed by phase 3 success.

Overall, it is our view that the accumulated evidence still supports the use of whole brain atrophy as an interim outcome measure in progressive multiple sclerosis trials.

Discordant results from phase 2 to phase 3 trials of the same intervention occur for many reasons—such as inherent variability in biological systems or insufficient precision of statistical estimates derived from small phase 2 trials—and do not necessarily discredit the interim outcome used to support progression to phase 3. Future research priorities, however, should include identifying whether novel biomarkers might more accurately predict clinical treatment effects for specific drug mechanisms, compared to whole brain atrophy. For example, for drugs such as tolebrutinib that target CNS compartmentalised inflammation, brain atrophy could be compared or combined with new imaging biomarkers that might be more specific to such pathology, such as slowly expanding lesions or positive rim lesions.^{51,52}

Ultimately, a single neuroprotective agent alone might not uniformly mitigate progressive biology across all individuals in a disease such as SPMS, in which there is a complex, dynamic, and heterogeneous pathobiology and multiple contributory mechanisms of disability worsening. For example, monotherapy targeting acid-sensing ion channels (amiloride), reducing glutamate release and antagonising voltage-dependent sodium channels (riluzole), improving mitochondrial energy metabolism (eg, fluoxetine, biotin, idebenone), and promoting remyelination (opicinumab) have not brought success despite well conducted clinical trials.¹ Multimodal combinations would seem to be indicated, although this will increase the side-effect profile and trial complexity.

This study is not without limitations. The COVID-19 pandemic had a profound impact upon clinical research and patients living with long-term conditions within the UK and worldwide. While national restrictions enforced episodic pauses in recruitment, the MS-STAT2 trial successfully continued follow-up during the pandemic, facilitated by existence of a validated remote collection method for the primary outcome (telephone EDSS).²⁶ The sensitivity analyses, however, showed that the primary result was unchanged when only including participants assessed in person before (baseline) and subsequently after (3 years) the pandemic, suggesting that the pandemic and the necessary remote data collection had minimal effect on the findings. Subgroup analyses also found no evidence of heterogeneity in treatment effects across epochs before, during, and after pandemic restrictions. The proportion of participants with remote assessment was also well balanced between treatment groups. We do note, however, the acceleration of progression during the COVID-19 period. Reasons for this increased progression might include deconditioning, withdrawal of physiotherapy, social isolation, and the effects of COVID-19 itself. This study is the first time that such impacts of the COVID-19 pandemic have been reported within an RCT framework, although similar findings have been reported in observational studies.⁵³

In total, around 2000 participants have now taken part in RCTs of statins in multiple sclerosis. Relapsing

multiple sclerosis studies of 789 participants randomly assigned equally to either simvastatin or atorvastatin as an add-on to β -interferon collectively have demonstrated no benefit in relapse rate reduction.⁵⁴⁻⁶⁰ With the reporting of the MS-STAT2 trial, we now also conclude definitively that simvastatin has no material therapeutic benefit in reducing progression in SPMS. Of course, this conclusion does not change the need to effectively treat vascular comorbidity in people with multiple sclerosis, especially given the evidence that people with multiple sclerosis are at higher risk of vascular events compared to those without multiple sclerosis.⁸ Statins remain an integral modality in both primary and secondary vascular prevention.

Contributors

JC, JMN, CF, RH, MB, HLF, SC, RN, SPa, EG, ST, OC, GG, JGr, and AJT researched and wrote the original grant application. All authors were involved in the set-up and running of the trial, and contributed to the writing of the manuscript. JBl represents the sponsor, developed the trial protocol, and contributed to writing of the manuscript. JMN, CF, EB, AH, and RH were involved in development of the statistical and health economic analysis facets of the trial, protocol design, and contributed to the writing of the manuscript. TW, NJ, MB, FDA, AB, AC, AD, SAM, and CW comprised the lead site clinical team working on the trial and contributed to the writing of the manuscript. RM and GB are the trial management team at the University College London Comprehensive Clinical Trials Unit and contributed to the writing of the manuscript. DL, EJ, and TA are operational research leads at their respective sites and contributed to the manuscript. SN and JBe are PPI representatives and critically reviewed the manuscript. ASH, GM, RG, MC, CH, JGa, LF, JH, CS, NPR, SK, SPI, SH, MM, TH, CY, ML, SKC, FA, DR, ES, PG, MD, AS, CR, ORP, NE, BS, IG, SC, HLF, and JC were site principal investigators and also contributed to the writing of the manuscript. EG represented the funder and contributed to writing of the manuscript. JC is the chief investigator for the trial, contributed to writing of the manuscript, and had final responsibility to submit the data for publication. All authors had access to the data and had final responsibility for the decision to submit for publication. The data was accessed and verified by JMN, CF, TW, JBl, GB, RM, and JC.

Declaration of interests

In the last 3 years, JC has received support from the Health Technology Assessment (HTA) Programme (National Institute for Health and Care Research; NIHR), the UK MS Society, the US National MS Society, and the Rosetrees Trust. He is supported in part by the National Institute for Health and Care Research, University College London Hospitals (UCLH) Biomedical Research Centre, London, UK. He has been a local principal investigator for a trial in multiple sclerosis funded by MS Canada. A local principal investigator for commercial trials funded by: Ionis and Roche; and has taken part in advisory boards/consultancy for: Biogen, Continuum Therapeutics, FSD Pharma, InnoCare, Pheno Therapeutics, and Roche. OC declares being NIHR Research Professor (RP-2017-08-ST2-004); over the past 2 years, member of independent data safety and monitoring board for Novartis; has received consulting fees or speaker honoraria from Lundbeck, Merck or Biogen; contributed to an advisory board for Biogen; she is Deputy Editor of *Neurology*, for which she receives an honorarium; has received research grant support from the UK MS Society, the NIHR UCLH Biomedical Research Centre, and the NIHR; and is vice-president of ECTRIMS (unpaid). HLF has received honoraria for advisory boards or educational activities from Merck, Novartis, and Roche. HLF has research grant support from the NIHR Health Technology Assessment Programme and Efficacy and Mechanisms Evaluation, UK MS Society, and the Horne Family Charitable Trust. She has been a local PI for multiple sclerosis clinical trials of an investigational medicinal product funded by Novartis, Roche, and Biogen Idec. LF has received honoraria for speaking or as an advisory board member from Biogen, Novartis, Merck, Sanofi Genzyme, and Roche and received support for attending educational meetings

from Biogen, Novartis, Merck, Sanofi Genzyme, and Teva. GG declares he has received compensation for serving as a consultant, speaker, or research support from Astoria Biologica, Biogen, BMS, Kiniksa, Merck, EMD Serono, Moderna, Sandoz, Sanofi, Roche, Genentech, Viracta, and Zenas BioPharma. IG declares that in the past two years he received research funding from Wessex Medical Research, Independent Research Fund Denmark, UK MS Society, The Binding Site, and NIHR; and conference and travel expenses from Novartis. NJ is a principal investigator on commercial multiple sclerosis trials sponsored by Roche, Sanofi, and Novartis. He has received speakers honoraria from Merck and travel congress sponsorship from Novartis. He has grant support from National Health and Medical Research Council (Australia), paid via his institution. MM has received travel support, speaker honoraria, or consultation fees from Merck-Serono, Novartis, and Roche. RN receives support from UK MS Society to Imperial College and Swansea university; is a trustee of the Multiple Sclerosis Trials Collaboration charity; and attended paid advisory boards for Novartis and Roche. SPI is founder, chief scientific officer, and shareholder (>5%) of Cambridge Innovation Technologies Consulting and is a consultant for Aspen Therapeutics, Secretome Therapeutics, Macomics, Solute Guard Therapeutics, and Astex Pharmaceutical. DR declares consulting, speaker fees, or support for conference attendance or travel received from Biogen, Celgene, MedDay, Hikma, Janssen, Merck, Neuraxpharm, Novartis, Roche, Sanofi Genzyme, and Teva. Additionally, research support paid to an institutional fund from the UK MS Society. AJT receives a fee from being Co-Chair, University College London (UCL)-Eisai Steering Committee drug discovery collaboration; German Aerospace Center, Heath Research (ERA-NET NEURON); consultancy from Sandoz Global Advisory and Novartis. Member, National Multiple Sclerosis Society (USA) Research Programs Advisory Committee; Clinical Trials Committee, Progressive MS Alliance; Board member, European Charcot Foundation; Editor in Chief, *Multiple Sclerosis Journal*; Editorial Board Member, *The Lancet Neurology*. AJT has received fees for academic reviews for Jockey Club College at City University of Hong Kong, Health Research Board Ireland, Sant Pau Biomedical Research Institute. AJT has received support from the UCL/UCLH NIHR Biomedical Research Centre. AJT received travel support from European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS), the European Charcot Foundation, Health Research Board Emerging Clinical Scientist Award, Polish Neurological Society, and Armin Curt Farewell Symposium. He receives no fee from being Chair (Scientific Ambassadors), Stop MS Appeal Board, UK MS Society; Research and Academic Counsellor, Fundació Privada Cemcat; Ambassador, European Brain Council. AJT additionally holds a patent for the MSIS-29 Impact Scale. SC is co-founder and director of Pheno Therapeutics and receives consultancy payments for this role. EG is head of clinical trials at the UK MS Society. FDA has received speaker honoraria, travel or conference support, or fees for advisor board participation from Neurology Academy, Coloplast, Janssen, Merck, Novartis, Roche, Sanofi. She is regional coordinator for the Oratorio Hand Trial (Hoffmann-La Roche) and principal investigator for commercial and academic trials (Alithios, O'Hand, Chariot-MS). JBl received salary payments from NIHR HTA programme for this work via his professional role at the UCL Comprehensive Clinical Trials Unit. JH declares research grant support paid to his institution from Roche, Sanofi, Novartis, Merck, Sandoz, and Verge genomics; licences for rating scales paid to his institution; personal consulting fees, honoraria, travel or conference support, or payment for expert testimony from Roche, Sanofi, and Merck. He participates on steering committees for CHARIOT-MS, ATTACK-MS, and for Sanofi. NR has received support for research fellowships or grants from Biogen and Sanofi; conference or travel support from Sanofi and Union Chimique Belge; participation in data monitoring boards from Sanofi and Neuraxpharm. He has personally owned shares in GlaxoSmithKline and AstraZeneca; and is President elect/President of the Association of British Neurologists. AC has received an advanced research contract from BBVA Foundation—Hospital Clinic Barcelona, and a Postdoctoral training fellowship from ECTRIMS. He has also received travel support from Americas Committee for Treatment and Research in Multiple Sclerosis. AB received a research grant from the Italian Society of Neurology, and a Magnetic Resonance Imaging in Multiple Sclerosis—ECTRIMS

fellowship; consulting fees from Merck Serono; speaker's honoraria from Merck Serono and Biogen; and travel support from Merck Serono. CR has received research grants from the UK Medical Research Council, Sanofi, Burden Neurological Society, University of Bristol, and Bristol Health Research Charity, and support for clinical research for the OCTOPUS trial (UK MS Society). CR has participated on a data safety monitoring board for the CCMR Two and NEuEoMS trials. Unpaid advisory roles with the UK MS Society, Burden Neurological Institute, Association of British Neurologists, and NICE HTA Assessment Group. CF received grant funding from the NIHR HTA Programme for this work. RG received support for scientific meetings, courses, and honoraria for advisory work, and travel support from Bayer, Biogen, Merck, Novartis, Janssen, UCB, and MIAC. TH held an NIHR Biomedical Research Council Senior Fellowship; received honoraria for various teaching courses from Ispen, and Pfizer; and support for attendingECTRIMS from Sanofi. DM received a development award from the Progressive MS Alliance; and honoraria from University of Calgary for a lecture. OP received travel expenses from Biogen, Bayer, Genzyme, Merck, Novartis, Roche, Sanofi, and Teva; participated on advisory boards or acted as speaker for Biogen, Bristol Myers Squibb, Janssen-Cilag, Merck, Neuraxpharm, Novartis, Roche, and Sanofi. MD received consulting fees from Sanofi, Merck, Novartis, Roche, Biogen, and BMS; honoraria from Novartis, Roche, Merck, and Biogen; payment for expert testimony from Biogen; travel support from Novartis, Sanofi, Merck, and Roche; participation on a data monitoring board with Roche and AB Science; leadership role with the UK MS Society as Co-chair UK MS Registers Executive Committee. RH received grants from NIHR DemPRU-QM, NIHR Evidence Synthesis, and NIHR Health Protection Research Unit; received consulting fees from Ministry of Justice, UK Health Security Agency, University of Nottingham, and QuidelOrtho; and leadership role on transforming health and care systems EU funding board as Chair of the Board. NE has received grants from Roche, PCORI, and the UK MS Society; received consulting fees from Merck and Roche; and conference travel support from Novartis and Sanofi. All other authors declare no competing interests.

Data sharing

All data requests should be submitted to JC for consideration in the first instance. Access to available fully anonymised data might be granted 12 months after publication, after review by JC and the sponsor (University College London). Requesters will be asked to complete an application form detailing specific requirements, rationale, and proposed use. A data-sharing agreement will need to be signed. Requested data will be made available, along with supporting documentation (eg, data dictionary) on a secure server.

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Sclerosis Clinical Research Chair at Departments of Medicine and Community Health and Epidemiology, Faculty of Medicine, Dalhousie University, Halifax, Canada. Finally, we thank all the MS-STAT2 investigators, a list of whom are provided in the appendix pp 159–62. LF's previous affiliation was University Hospitals Sussex NHS Foundation Trust, Brighton, UK, her current affiliation is Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK. We particularly here record the death of our friend and colleague Dr Matt Craner in 2024.

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