








BMJ Open Evaluating the effectiveness of simvastatin in slowing the progression of disability in secondary progressive multiple sclerosis (MS-STAT2): protocol for a multicentre, randomised controlled, double-blind, phase 3 clinical trial in the UK

James Blackstone ¹, Thomas Williams,² Jennifer M Nicholas,³ Ekaterina Bordea,¹ Floriana De Angelis,² Alessia Bianchi,² Alberto Calvi,² Anisha Doshi,² Nevin John,² Sean Apap Mangion,² Charles Wade,² Rachel Merry,¹ Gil Barton,¹ Dawn Lyle,⁴ Elisabeth Jarman,⁵ Don Mahad,⁴ Abdullah Shehu,⁶ Tarunya Arun,⁶ Gavin McDonnell,⁷ Ruth Geraldes,⁸ Matthew Craner,⁸ Charles Hillier,⁹ Jeban Ganesalingam,¹⁰ Leonora Fisniku,¹⁰ Jeremy Hobart,¹¹ Cord Spilker,¹² Neil Robertson,¹³ Seema Kalra,¹⁴ Stefano Pluchino,^{15,16} Sreedharan Hari Krishnan,¹⁷ Miriam Mattoscio,¹⁸ Timothy Harrower,¹⁹ Carolyn Young,^{20,21} Martin Lee,²² Suresh Chhetri,²³ Fayyaz Ahmed,²⁴ David Rog,²⁵ Eli Silber,²⁶ Paul Gallagher,²⁷ Martin Duddy,²⁸ Agne Straukiene,²⁹ Richard Nicholas,³⁰ Claire Rice,³¹ Stuart J Nixon,³² Judy Beveridge,³² Annie Hawton,³³ Susan Tebbs,¹ Marie Braisher,² Gavin Giovannoni ³⁴, Olga Ciccarelli,² John Greenwood,³⁵ Alan J Thompson,² Rachael Hunter ³⁶, Sue Pavitt,³⁷ Owen Pearson,³⁸ Nikos Evangelou,³⁹ Basil Sharrack,⁴⁰ Ian Galea ⁴¹, Siddharthan Chandran ^{4,42}, Helen L Ford ⁴³, Chris Frost,³ Jeremy Chataway ^{2,44}

To cite: Blackstone J, Williams T, Nicholas JM, *et al*. Evaluating the effectiveness of simvastatin in slowing the progression of disability in secondary progressive multiple sclerosis (MS-STAT2): protocol for a multicentre, randomised controlled, double-blind, phase 3 clinical trial in the UK. *BMJ Open* 2024;**14**:e086414. doi:10.1136/bmjopen-2024-086414

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (<https://doi.org/10.1136/bmjopen-2024-086414>).

Received 14 March 2024
Accepted 16 August 2024



© Author(s) (or their employer(s)) 2024. Re-use permitted under CC BY. Published by BMJ.

For numbered affiliations see end of article.

Correspondence to

Prof Jeremy Chataway;
j.chataway@ucl.ac.uk

ABSTRACT

Introduction There remains a high unmet need for disease-modifying therapies that can impact disability progression in secondary progressive multiple sclerosis (SPMS). Following positive results of the phase 2 MS-STAT study, the MS-STAT2 phase 3 trial will evaluate the efficacy and cost-effectiveness of repurposed high-dose simvastatin in slowing the progression of disability in SPMS.

Methods and analysis MS-STAT2 will be a multicentre, randomised, placebo-controlled, double-blind trial of participants aged between 25 and 65 (inclusive) who have SPMS with an Expanded Disability Status Scale (EDSS) score of 4.0–6.5 (inclusive). Steady progression rather than relapse must be the major cause of increasing disability in the preceding 2 years.

Participants will be allocated to simvastatin or placebo in a 1:1 ratio. The active treatment will be 80 mg daily, after 1 month at 40 mg daily. 31 hospitals across the UK will participate.

The primary outcome is (confirmed) disability progression at 6 monthly intervals, measured as change from EDSS

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ The MS-STAT2 trial will be the first phase 3 randomised controlled trial to assess the effectiveness of repurposed simvastatin compared with placebo in slowing the progression of disability in secondary progressive MS as a potential neuroprotective agent.
- ⇒ It will be the largest ever investigator-initiated phase 3 trial in progressive MS.
- ⇒ There will be a range of trial sites from neuroscience centres to district general hospitals.
- ⇒ It will have a relatively high age range (up to 65 years) to increase inclusivity with significant patient and public involvement.
- ⇒ A limitation is those who are required to be on a statin for their general health are ineligible to participate.

baseline score. Recruitment of 1050 participants will be required to achieve a total of 330 progression events, giving 90% power to demonstrate a 30% relative reduction in disability progression versus placebo. The follow-up

period is 36 months, extendable by up to 18 months for patients without confirmed progression.

Clinician-reported measures include Timed 25 Foot Walk; 9 Hole Peg Test; Single Digit Modalities Test; Sloan Low Contrast Visual Acuity; Relapse assessment; modified Rankin Scale and Brief International Cognitive Assessment For Multiple Sclerosis. Patient-reported outcomes include MS-specific walking, fatigue and impact scales. A health economic analysis will occur.

Ethics and dissemination The protocol was approved by the London-Westminster REC (17/LO/1509). This manuscript is based on protocol version 8.0, 26 February 2024. Trial findings will be disseminated through peer-reviewed publications and conference presentations.

Trial registration numbers [NCT03387670](https://www.clinicaltrials.gov/ct2/show/study/NCT03387670); [ISRCTN82598726](https://www.clinicaltrials.gov/ct2/show/study/ISRCTN82598726).

INTRODUCTION

Multiple sclerosis (MS) is the most common acquired disabling neurological disease affecting adults in temperate latitudes. It is a progressive disorder of the brain and spinal cord (central nervous system) and with current figures (2023) recording a prevalence of 135 000 in the UK and 2.9M globally.¹

Secondary progressive MS (SPMS) is characterised by a range of severe problems affecting walking, balance, manual function, vision, cognition, pain, bladder and bowel function.^{2–4} Rates of conversion from relapsing-remitting MS (RRMS) to SPMS vary depending on definitions used, access to disease-modifying therapy (DMT) and the time period observed. Estimates vary on the risk of conversion, but a recent study reported that the median time from RRMS onset to SPMS is around 30 years⁵ while a separate meta-analysis of SPMS prevalence estimated this would affect up to 50 000 individuals in the UK.⁶ SPMS also has significant financial costs for the National Health Service (NHS), patients and their caregivers; in the UK, the estimated mean annual cost per patient from the societal perspective ranges between £22 000 (Expanded Disability Status Scale, EDSS 4–6.5) and £34 000 (EDSS 7–9).^{7,8}

Unlike RRMS, where there is an increasing number (over 15) of DMTs, therapeutic options for those with SPMS are very limited.^{9,10} Siponimod is the only commonly used DMT licensed in the UK for SPMS, but its use is restricted to patients with recent activity (patients with recent inflammatory disease activity, characterised by relapses or new/enhancing MRI lesions). There is a clear lack of effective treatments to impact disease progression.¹¹

The MS-STAT phase 2 trial randomised 140 people with SPMS to receive high-dose simvastatin (80 mg/day) or placebo for 2 years. It showed that simvastatin was safe, well tolerated and reduced the rate of annualised brain atrophy by 43% over 2 years. This was supported by positive effects on some secondary outcomes, including clinician-reported (EDSS) and patient-reported (Multiple Sclerosis Impact Scale-29 v2, MSIS29v2) measures.¹²

Despite previous experimental data showing that statins possess immunomodulatory effects in MS,^{13–16} the MS-STAT trial did not demonstrate any shift towards

a more favourable systemic immunological signal,¹² suggesting that alternative mechanisms prevail. Statins suppress astroglial and vascular activation,^{17–19} improve vascular perfusion and function,^{20–22} and attenuate oxidative damage which protects the brain from chronic hypoxic stress. This is especially germane considering evidence that dysfunctional/reduced blood flow in MS may predispose the tissue to damage.^{23–27} In support of this, patients with later-stage MS exhibit vascular^{28–30} and brain parenchymal cell dysfunction.^{19,31–33} It is also clear that there is an increase in prevalence of vascular disease in MS, which impacts on disease severity.^{34,35}

Therefore, while the cholesterol-dependent actions of statin treatment have been implicated in the past, most evidence continues to support a predominant role for cholesterol-independent processes. Indeed, using a modelling approach from the MS-STAT trial, it was predicted that the beneficial effect was independent of the reduction in total systemic cholesterol levels, signifying the involvement of upstream intermediate metabolites.³⁶ Interestingly, a recent Mendelian Randomisation study, looking at the risk of developing MS, implicated the Rho GTPase pathways,³⁷ felt to be central to earlier mechanistic animal work.^{38,39}

METHODS AND ANALYSIS

Trial objective

Following the promising results of the MS-STAT phase 2 trial,¹² the MS-STAT2 trial has been designed to determine whether simvastatin can slow the time to confirmed disability progression (CDP), based on the current regulatory standard of confirmed EDSS progression.⁴⁰ The primary objective is to compare the effect of daily use simvastatin (80 mg) versus placebo on disability progression at 6 monthly intervals in patients with SPMS, based on change in EDSS score compared with baseline.

Trial design and setting

MS-STAT2 will be a randomised, multicentre, double-blinded, prospective, parallel-group trial design. The intervention will be oral simvastatin 80 mg vs placebo for patients with SPMS. [Figure 1](#) illustrates the participant pathway. Online supplemental table 1 outlines the trial activities to be conducted, including the clinician and patient-reported outcomes that will be collected. The trial will be conducted at 31 UK NHS hospitals, a mix of trial sites from neuroscience centres to district general hospitals. Participating hospitals will be geographically spread between England, Scotland, Wales and Northern Ireland. The trial will commence in May 2018 and conclude in August 2024.

Eligibility criteria

Participants will be aged between 25 and 65 years (inclusive) who fulfil the revised McDonald criteria for MS,^{41–43} and have SPMS.^{44,45} Steady progression rather than relapse must be the major cause of increasing disability

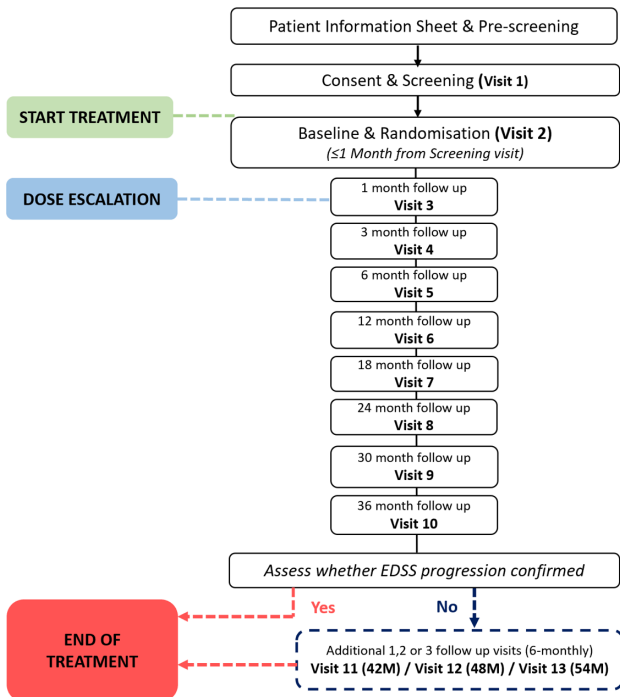


Figure 1 Participant timeline. EDSS, Expanded Disability Status Scale.

in the preceding 2 years. The inclusion and exclusion criteria are set out in [box 1](#).

Recruitment and consent

Participating sites will be centres of expertise in MS and trials in MS; have long-term links with the local MS patient population and will have records of patients who may be eligible to participate.

A national-level registration of interest website will be set up to allow patients to register their interest in the trial, and these details will be transferred to the relevant site trial team for further contact.

In prescreening patients (usually by telephone), sites will provide prospective recruits with the trial's patient information sheet, and then schedule a face-to-face clinic meeting if the patient expresses interest and appears to meet the eligibility criteria.

At a screening visit, participants will be informed of the aims, methods, benefits and potential risks of involvement in the trial and give documented and recorded informed consent prior to any trial-specific procedures being carried out.

Participants are permitted to either be taking newly licensed DMTs at the time of trial commencement (ie, siponimod) or to begin such use as a concomitant medication while in trial.

A lipid profile will be completed at screening only.

Treatment allocation

Participants will be randomised in a 1:1 ratio between simvastatin or placebo, based on a minimisation algorithm that incorporates the following factors: sex (male/female); age (< or ≥45 years); EDSS baseline score (≤5.5 or

Box 1 Inclusion and exclusion criteria

Inclusion criteria

Patients with a confirmed diagnosis of multiple sclerosis (MS) who have entered the secondary progressive stage. Steady progression rather than relapse must be the major cause of increasing disability in the preceding 2 years. Progression can be evident from either an increase of at least one point if Expanded Disability Status Scale (EDSS) baseline score <6, or an increase of 0.5 point if baseline EDSS score is ≥6, or clinical documentation of increasing disability. EDSS 4.0–6.5 (inclusive).

Aged 25–65 years old.

Patients must be able and willing to comply with the terms of this protocol.

Provide written informed consent.

Exclusion criteria

Relapse within 3 months of baseline visit. Patients will be eligible where 3 months from the final day of the relapse, have elapsed by the date of the baseline visit.

Patients who have been treated with steroids (intravenous and/or oral) due to MS relapse/progression within 3 months from the final day of relapse to the baseline visit. These patients may undergo a further screening visit once the 3-month window has expired and may be included if no steroid treatment has been administered in the intervening period.

(Patients on steroids for another medical condition may be included in the trial provided the steroid prescription is not for MS relapse/progression).

Significant organ comorbidity, for example, cardiac failure, renal failure, malignancy.

Screening levels of alanine aminotransferase/aspartate aminotransferase or creatine kinase ≥3×upper limit of normal.

Current use of a statin; or any use within the last 6 months.

Medications that interact unfavourably with simvastatin as outlined in the current summary of product characteristics (Summary of Medicinal Product Characteristics); including but not limited to CYP3A4 inhibitors (eg, itraconazole, ketoconazole, posaconazole, voriconazole, fluconazole, HIV protease inhibitors (eg, nelfinavir), boceprevir, erythromycin, clarithromycin, telithromycin, telaprevir, nefazodone, fibrates (including fenofibrates), nicotinic acid (or products containing niacin), azole antifungal preparations, macrolide antibiotics, protease inhibitors, verapamil, amiodarone, amlodipine, gemfibrozil, ciclosporin, danazol, diltiazem, rifampicin, fusidic acid, elbasvir, grazoprevir, ticagrelor, daptomycin, grapefruit juice or alcohol abuse.

Primary progressive MS.

Diabetes mellitus type 1.

Uncontrolled hypothyroidism.

Female participants who are pregnant or breast feeding. Women of childbearing potential who are unwilling or unable to use an acceptable method to avoid pregnancy for the entire study period, and up to 4 weeks after the last dose of study drug.

Use of immunosuppressants (eg, azathioprine, methotrexate, ciclosporine) or disease-modifying therapies (avonex, rebif, betaferon, glatiramer) within the previous 6 months.

Use of mitoxantrone, natalizumab, alemtuzumab, daclizumab or other monoclonal antibody treatment, if treated within the last 12 months.

Use of fingolimod, dimethyl fumarate, teriflunomide, cladribine within the last 12 months.

Use of other experimental disease-modifying therapy within the last 6 months.

Commencement of fampridine ≤6 months from the day of randomisation.

Continued

Box 1 Continued

Concurrent participation in another clinical trial of an investigational medicinal product or medical device.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption.

≥6); whether participants are taking newly licensed (2017 onward) DMTs for SPMS; and trial site. An independent and secure online randomisation service (SealedEnvelope.com) will be used by delegated site staff members to directly allocate participants to a treatment arm. Descriptive information (month and year of birth, initials and trial identifier) will be also entered to ensure randomisation allocation matches the intended participant.

Blinding

All participants, site investigators (including pharmacy) and the trial sponsor team will be blinded to treatment allocation. Only the randomisation service and trial statisticians have access to unblinded treatment allocations during trial recruitment and follow-up.

On randomisation, a five-digit code will be issued to site staff that identifies a blinded bottle of either simvastatin or placebo according to the participant's allocation. A hard copy of the code will be taken with the prescription to site pharmacy for direct issuance to the participant. Subsequent bottles ('maintenance kits') of simvastatin or placebo will be ordered using the same online service and issued to participant on the same basis as at randomisation.

It is not possible to ascertain from the issuance of kit codes which treatment arm a participant, or group of participants, at any site, is on. Patients will be unblinded as to their treatment arm following the final database lock for trial analysis. There will be a procedure in place for emergency unblinding.

INTERVENTION**Form**

Oral Sandoz simvastatin 40mg film-coated tablets or matching placebo.

Dosage

Participants will receive either simvastatin 80mg (initially 40mg at randomisation, then escalated after 1 month) or the same quantity of placebo (of the same colour/size), taken once daily at night.

Duration

Participants will continue on their allocated treatment arm for between 36 and 54 months. Those who have not experienced CDP by the 36-month point will be offered a further period of follow-up, if they are at a site participating in the trial extension period (see the 'Discussion' section). Participants in the extension period will remain on their blinded intervention for a further 6–18 months

beyond the 36-month time point, dependant on the time remaining before the end of overall trial follow-up. Participants who discontinue treatment will continue to be followed up unless they withdraw consent from participation in the trial.

Dose modification and stopping

The dose may be varied for patients experiencing hepatic effects, myopathy/rhabdomyolysis or other adverse events at the principal investigator's discretion. Where elevated alanine aminotransferase (ALT), aspartate aminotransferase (AST) or creatine kinase (CK) levels are sustained at $\geq 3 \times$ upper limit of normal (ULN), it is recommended that the dose is lowered (from 80mg (active/placebo) to 40mg (active/placebo)), with rechallenge at the higher dose possible after parameters return to normal. For ALT, AST or CK levels $\geq 5 \times$ ULN, trial medication should be stopped, with rechallenge only permissible where the intervention was clearly determined to be non-causally related (eg, another intercurrent medication or infection, which has now resolved, produced the biochemical abnormalities).

Outcomes**Primary outcome**

The primary outcome will evaluate the effect of daily use of simvastatin (80mg) versus placebo on disability progression at 6-monthly intervals in patients with SPMS, based on change in EDSS score compared with baseline. Progression of disability will be defined as an increase of at least 1 point if the baseline EDSS score < 6 , or an increase of 0.5 point if EDSS score ≥ 6 . The initial disability progression event is finalised as positive if the disability is sustained and confirmed ≥ 6 months later. This allows for disability confirmation to take place if a visit is missed. This is termed CDP. The date of progression (if confirmed) will be the initial date of the progression event. EDSS is generally assessed in person, but there will be capacity for this to be collected remotely via the telephone.⁴⁶ Time to first CDP will be compared between the simvastatin and placebo arms over treatment of up to 54 months. EDSS assessment will be performed by a blinded assessor, in line with the current version of the neurostatus scoring guidance (v04/10.2)

Secondary outcomes

Clinician-reported secondary outcomes will include Timed 25 Foot Walk (T25FW); 9 Hole Peg Test (9HPT); Single Digit Modalities Test (SDMT); Sloan Low Contrast Visual Acuity (SLCVA); Relapse assessment; modified Rankin Scale (mRS) and Brief International Cognitive Assessment For Multiple Sclerosis comprising SDMT, California Verbal Learning Test-II (CVLT-II) and Brief Visuospatial Memory Test-Revised (BVMTR).

Patient-reported outcomes will include MSIS-29v2; Multiple Sclerosis Walking Scale-12 v2 (MSWS-12v2); Modified Fatigue Impact Scale - 21 (MFIS-21); Chalder Fatigue Questionnaire (CFQ).

Health economic outcomes

For the health economic analysis, the EuroQoL EQ-5D 5 level (EQ-5D-5L) and a bespoke resource use measure (RUM), that is, the Client Services Receipt Inventory (CSRI), will be used.

Trial schedule

Online supplemental table 1 presents the trial schedule of assessments. Following baseline/randomisation, where a full set of clinical assessments and patient-reported questionnaires will be completed, participants will attend the clinic for safety monitoring and dose escalation at 1 month. At 3 months, participants have a telephone check-up (with safety bloods arranged locally), and then will have further assessment visits at 6-monthly intervals from 6 months postrandomisation onward. Where participants are unable to attend 6-monthly follow-ups (such as due to COVID-19-related issues or participant logistics), a telephone-EDSS assessment will be undertaken,⁴⁶ together with remotely collected patient-reported outcomes and locally performed safety bloods.

In terms of clinician-reported outcomes, the EDSS, 9HPT and T25FW will be performed 6 monthly; the SDMT, SLCVA and mRS annually; and CVLT-II and BVMT-R at baseline and the 36-month visits only. For patient-reported outcomes, the EQ-5D-5L and CSRI will be completed 6 monthly; with the CFQ, MFIS-21, MSIS-29v2 and MSWS-12v2 completed annually.

Participants will be evaluated at the 36-month time point visit to determine whether they have experienced EDSS CDP. Those participants yet to have CDP will be asked to consent to continued follow-up into the extension phase, at sites which agree to take part in the extension, as outlined in the 'Intervention' section.

At the lead site (University College London Hospitals Trust) only, additional subsidies will be conducted to investigate MRI, biomarker and optical coherence tomography outcomes.

Power and sample size

In order to have 90% power to demonstrate a 30% relative reduction in disability progression for simvastatin versus placebo, at the conventional 5% significance level, the trial will require a total of 330 progression events. This will be achieved by recruiting 1050 participants with 525 enrolled on each treatment arm. Individual participant trial duration will be a minimum of 36 months (core) and up to a further 18 months (extension) if there is no confirmed progression event by 36 months. This assumes that the placebo progression rate will be 40% by 36 months and 49% by 54 months⁴⁷⁻⁵⁰ and allows for 20% loss to follow-up by 36 months and 32% by 54 months (among those who are eligible for the extension). This is equivalent

to a progression rate of 8% per 6 months among those who have yet to experience progression.

ANALYSES

Statistical analysis

The primary statistical analysis will be based on all participants as randomised, irrespective of subsequent compliance with allocated treatment (intention-to-treat analysis). A secondary per-protocol analysis will be carried out including only participants who were able to comply (see the 'Compliance' section) with simvastatin or placebo treatment.

Primary outcome

The primary analysis will be a comparison of the time to EDSS initial disability progression (if confirmed ≥ 6 months later) between the simvastatin and placebo arms. HRs and 95% CIs will be calculated using a Cox proportional hazards model and Kaplan-Meier curves produced. The time scale used for survival analysis will be time since randomisation. Participants will be censored if they die, are lost to follow-up, withdraw from the trial or at the final patient visit at which confirmed progression could take place. The model will allow for between-centre variability by stratification by site (baseline hazard allowed to differ by site). In addition, other variables included in the minimisation process will be included as fixed effects. The assumptions underlying the Cox model will be assessed and if there is clear non-proportionality, HRs will be presented separately for the relevant time periods.

Secondary outcomes

The proportions of participants with confirmed progression at 36 months on the composite (multicomponent) disability progression outcome (EDSS, T25FW or 9HPT), and proportions with confirmed progression on the individual outcomes making this composite, will be compared between arms using logistic regression adjusting for the minimisation variables as fixed effects. Proportions with progression on mRS at 36 months will also be compared using logistic regression, adjusting for the minimisation variables. ORs and 95% CIs will be presented along with the p value for a Wald test for the difference between treatment groups.

Baseline to 36 months change in continuous clinician and patient-reported outcomes will be compared between groups using linear mixed models for repeated measures. For each outcome, the difference in mean of the outcome at 36 months will be reported alongside 95% CIs and the two-sided p value. Analysis of MSIS-29v2, MSWS-12v2, MSFIS-21 and CFQ will use data recorded at all available visits. Analysis of MSFC, T25FW, 9HPT, SLCVA, CVLT-II, BVMT-R and SDMT will use data recorded at baseline and 36 months (due to COVID-19 as described below). The dependent variable will be the outcome at each time point. Treatment group will be included as predictor, with treatment by visit interaction,

but at baseline the treatment effects will be constrained to be zero, which is essentially equivalent to adjusting for baseline using analysis of covariance (ANCOVA).⁵¹ An unstructured covariance matrix for the residuals will be used to allow for correlation between repeated measures on an individual. The minimisation variables, and their interactions with visit, will be included as fixed effects. If parametric assumptions for the linear regression model are substantially violated, bias-corrected and accelerated bootstrap confidence intervals will be used for inference.

The relapse rate up to 36 months will be compared between groups using negative binomial regression adjusting for the minimisation variables as fixed effects. Numbers of relapses by grade, adverse events, serious adverse events and notifiable adverse events will be tabulated by treatment group.

Compliance

Participants will be considered to be compliant with their randomised intervention if the summary measure of compliance is over 90%, which means they took 80 mg/2 tablets on at least 90% of days over the first 36 months of follow-up, or until the date of confirmed progression, death or withdrawal if these happened before 36 months. A secondary measure of compliance will consider participants compliant if they took either high (80 mg/2 tablets) or low (40 mg/1 tablet) dose on at least 90% of days.

Interim analyses

The independent data monitoring committee (IDMC) will consider stopping for safety if there is evidence that the trial treatment is worse than placebo alone with a $p < 0.01$ for all-cause deaths. The IDMC will consider stopping for an efficacy-based $p < 0.001$ for a difference between the treatment groups on the primary outcome of 6 months confirmed EDSS progression. Additionally, the IDMC will consider stopping for futility based on recruitment of less than 53% of the final sample size at 15 months after starting the trial.

Missing data

Missing data will be identified and efforts made to obtain these data. Characteristics of a total number of participants withdrawing and reasons for withdrawal will be tabulated by the treatment group and compared with those with complete data. In the event of substantial differences in withdrawal patterns being found, further sensitivity analyses will be carried out to investigate the robustness of the results.

Analysis plan

A detailed statistical analysis plan has been written and signed off. All statistical tests will use a two-sided p value of 0.05 unless otherwise specified. Statistical analysis will be performed by using Stata v17.0 (StataCorp).

Impact of COVID-19 on patient characteristics and trial outcomes

The impact of the COVID-19 pandemic on the trial data will be considered by comparing data collected during three periods, which were chosen based on when public health restrictions were in place in the UK:

- ▶ Prior to 16 March 2020—before restrictions.
- ▶ From 16 March 2020 to 19 July 2021—during restrictions.
- ▶ After 19 July 2021—after restrictions were removed.

Baseline characteristics will be tabulated by treatment group and by mode of visit attendance (in-person vs remote) for visits occurring in the three periods identified above.

A sensitivity analysis will be performed for the primary outcome to assess the impact of COVID-19. This will compare progression at 36 months in trial participants who had EDSS collected at both baseline and month 36 in-person visits during time periods when COVID-19-related public health restrictions were not in force.

A sensitivity analysis will also be performed to compare patient-reported outcomes between trial arms using only data from visits at baseline and 36 months that were collected during periods where public health restrictions were not in force.

In addition, subgroup analyses will examine whether there is evidence that the treatment effect on the primary or secondary outcomes differed between the three time periods, by including a period of treatment interaction in the relevant model.

Health economics analysis

A treatment that slows progression could represent a highly cost-effective use of NHS resources with the high costs of SPMS and very low cost of simvastatin. A cost-utility study will be carried out to assess the incremental cost per quality-adjusted life-year (QALY) gained from the perspective of the NHS and personal social services (PSS). Cost utility will be estimated for the 'within trial' period and also for the lifetime of the patient using a model-based approach.

The within-trial economic evaluation will estimate cost-effectiveness of simvastatin for the first 36 months of the trial period. Health service costs associated with SPMS include inpatient admissions (particularly during relapses or intercurrent illness), outpatient contact (including neurology consultants, MS specialist nurses and allied healthcare professionals), and GP and community care (such as physiotherapy and social worker appointments). Patient resource use will be assessed using the CSRI, a self-complete RUM and using patient records. This RUM will be modified according to the needs of people with SPMS and will be administered at baseline and 6-monthly intervals.

QALYs will be estimated, 6 monthly, using the EQ-5D-5L using the area under the curve approach. Utility scores will be calculated using UK-specific tariffs and adjusting for baseline differences in patients in the

trial arms if necessary. In addition, given current uncertainties regarding the appropriateness of the EQ-5D-5L for people with SPMS,⁵² the MSIS-29v2,⁵³ a condition-specific measure will be considered for estimating QALYs through methods available in the literature.⁵⁴

The primary within-trial analysis will be intention-to-treat analysis and the secondary analysis will be per protocol analysis in line with the main statistical analysis. Results will be estimated as the incremental cost-effectiveness ratio (ICER) where data will be drawn as far as possible from the trial. Within-trial CIs for mean costs and QALYs will be calculated using a non-parametric bootstrap with replacement.⁵⁵ The results of the non-parametric bootstrap will be presented on a cost-effectiveness plane. The bootstrap replications will be used to construct a cost-effectiveness acceptability curve, which will show the probability that the intervention is cost-effective for different values of the NHS' willingness to pay for an additional QALY. Appropriate methods for dealing with missing trial data such as multiple imputation will be applied. We will assess the impact of COVID-19 on the ICER in the same fashion as the main statistical analysis.

The decision analytical model will take the form of a Markov model and estimate costs and benefits over the lifetime horizon of the patient to capture the progression of the condition beyond the trial period. The model will include EDSS states and a death state. A secondary analysis from a societal perspective will be undertaken which will consider additional costs borne by the patient such as time off work. Data to populate the model will be obtained from the trial and from published sources. Long-term costs and health outcomes will be discounted using discount rates recommended by the UK National Institute for Health and Care Excellence.⁵⁶

All analyses will conform to recommended economic evaluation methods.⁵⁶ All methods will be described in a detailed health economic analysis plan.

MONITORING

Oversight

A trial steering committee and independent data monitoring committee will be formally responsible for the oversight of the trial and ensuring it is conducted in compliance with Good Clinical Practice (GCP), and the relevant regulatory and ethics committee approvals.

The trial management group (TMG) will be responsible for the execution of the trial.

UCL is the sponsor for the trial, with delegated authority to the UCL Comprehensive Clinical Trials Unit (UCL CCTU).

Safety event reporting

Site teams will report to sponsor all adverse events (irrespective of severity, causality or expectedness in relation to the trial intervention), which will take place from the time of commencement of the intervention to end of patient pathway. Adverse events meeting the

'serious' threshold (SAEs) will be subject to expedited reporting to sponsor (immediately and no later than 24 hours from site awareness) in line with the relevant UK regulations.

Additionally, notifiable adverse events (NAEs) for hepatotoxicity or myalgia (supported by laboratory abnormalities of ≥ 3 times ULN for ALT/AST, respectively) are reportable to the sponsor within the same timelines as for SAEs. Clinical review of all SAEs and NAEs will be undertaken by the sponsor, with events classified as serious adverse reactions (SARs) or suspected unexpected serious adverse reactions (SUSARs) will be onward reported in line with the relevant UK regulations and ethical approvals.

Expectedness will be determined using Section 4.8 of the approved Summary of Medicinal Product Characteristics (SmPC) for simvastatin.

Pregnancy is not an SAE, but following the initiation of the trial medication, if a female participant becomes pregnant, or female partner of a male participant becomes pregnant, then a trial pregnancy notification form will be sent to the sponsor immediately. Pregnancies will be followed up; untoward outcomes will be assessed against trial safety reporting criteria.

Audit

Clinical trial monitoring will be conducted by the trial coordinating team utilising both a 'central' monitoring approach combined with risk-adaptive 'on-site' monitoring at NHS clinical and pharmacy sites. Central data review will be used to trigger additional on-site visits where appropriate, but as a minimum, all sites will be monitored in person at least once with thresholds established for planned increase of frequency (eg, proposed site sample size). Central monitoring will be performed by the data manager, and on-site monitoring (including source data verification) will be undertaken by the trial manager, both based at the UCL CCTU. A monitoring plan will be created and updated at least annually, with UCL CCTU Quality Management Group oversight.

Emergency contacts and unblinding

All recruited participants will be given a card with contact details of the clinical trial team including an emergency contact available out of hours. In the event unblinding becomes necessary, this will be performed through the 24 hours, 7 days a week web-based service offered by the trial's randomisation service. It is expected that emergency unblinding will only be performed for those patients experiencing a medical emergency for which the clinical management will require knowledge of the participant's treatment allocation. It is anticipated that for the majority of clinical care instances, appropriate management can proceed with the assumption that the patient has been treated with simvastatin without needing to unblind the participant.

Withdrawal of trial participants

Participants may withdraw from trial participation at any time without prejudicing their right to NHS standard of care. Participants who discontinue the trial intervention will remain in follow-up unless they withdraw consent. Data from withdrawn participants will be included in the analysis unless they specifically withdraw consent for its use.

Patient and public involvement

MS-STAT2 has a strong patient and public involvement (PPI) strategy with significant contributions from the UK Multiple Sclerosis Society (UK MSS) PPI representatives and members of the UK MSS-PPI Forum to maximise patient benefit. Essential feedback provided on factors that could have an impact on participation such as age, entry disability, trial schedule and disability fluctuation have been taken into consideration and have been embedded in the protocol to ensure that it is acceptable to the patient community. PPI input will facilitate retention in the trial.

The UK MSS and forum will work closely with the research team to maximise participant retention by codeveloping a tailored communication strategy including making use of the existing UK MSS programme of events and publications to promote the trial to people living with MS. They will also explain the importance of minimising drop-out and encouraging UK MS Register enrolment.

Highly experienced PPI representation is also embedded into the operational functioning of the trial, through membership of both the trial management group and trial steering committees.

Ethics and dissemination

Data management and confidentiality

All trial documentation at site will be held in restricted access areas and stored securely by the site trial teams. Trial data will be initially entered onto paper case report forms (CRFs) and then entered by sites into a secure, validated online database (Elsevier MACRO V.4.0) and accessible only by delegated team members of that site, and by delegated staff from the coordinating centre at UCL CCTU.

CRFs for the trial will identify participants using a unique five-digit trial identifier, month and year of birth and initials. Under the UK Data Protection Act 2018, the latter identifiers will be considered as personally identifying and will be treated as such by both the site team and coordinating centre team.

Where written communication (eg, data queries) on individual patient cases is necessitated between sites and the coordinating centre, only the trial identifier should be used in the first instance.

Any transfer of documentation containing personally identifying data between site and coordinating centre will be subject to AES-256 industry-standard encryption.

Patient consent

All MS-STAT2 participants will need to provide informed consent as per the principles of GCP (as defined in the UK Medicines for Human Use (Clinical Trials) Regulations SI 2004) prior to any trial-specific procedures being undertaken. Participants will also agree to sponsor review of their medical records for clinical trial monitoring or inspection purposes.

Ethical approval and dissemination

The National Research Ethics Service Committee (London, Westminster) reviewed the trial protocol and materials to be given to patients (approved 9 October 2017, REC ref 17/LO/1509). This article refers to the current protocol (V.8.0, 26 February 2024). Online supplemental appendix 1 lists subsequent protocol amendments with reasons.

The findings of this trial will be disseminated through peer-reviewed publications and conference presentations. There will be a close communication strategy developed with the UK MSS and full PPI engagement.

Access to data

Data will be stored on an encrypted and password-protected database. Site staff will have direct control of their own site's data.

Where future analyses are proposed, these will be considered by the trial's publications committee with appropriate data sharing formal agreements to be put into place.

DISCUSSION

Several trial design changes have been required since the commencement of trial recruitment in 2018 (see online supplemental appendix 1). We discuss here, two key modifications to facilitate understanding of the Protocol V.8.0 as described above: (1) the addition of an extension period for participants not yet achieving CDP by month 36 and (2) the need to update some trial analyses in light of the COVID-19 pandemic period.

The original trial design allowed for a fixed 36-month period on IMP (with an additional 3-month period allowable for participants with initial disease progression at month 36 to allow for confirmation of such progression). Following permission of the trial steering and independent data monitoring committees, the team amended the protocol in February 2021 to permit a longer duration of follow-up (remaining on blinded trial drug/placebo) for participants who had not had CDP by month 36. The expectation was to capture the necessary number of primary outcome events critical to achieving adequate power on the trial while using a smaller than anticipated sample of patients: 1180 in the original design, revised to 1050 in the revised design, with an extension period of up to 54 months, dependent on the time remaining until last participant visit. The overwhelming majority of sites (n=21) were able to participate in this, though a handful

of lower recruiting sites reported lacking additional resource, and several sites commenced recruitment too late to enter participants into the extension period of the patient pathway.

The COVID-19 pandemic in the UK proved challenging for trial recruitment: no recruitment activity was either permitted or viable for several months in the summer of 2020. Moreover, participant access to trial sites was highly restricted, and as a consequence, the ability to be assessed for face-to-face secondary clinical outcomes, particularly T25FW, 9HPT, SLCVA, SDMT, CVLT-II, BVMTR. Following trial management team review in 2022 of the rates of postbaseline missing data for these outcomes, the decision was taken to move to a binary classification of confirmed progression by month 36 for these variables.

Author affiliations

- ¹Comprehensive Clinical Trials Unit, University College London, London, UK
- ²Queen Square Multiple Sclerosis Centre, Department of Neuroinflammation, UCL Queen Square Institute of Neurology, Faculty of Brain Sciences, University College London, London, UK
- ³Medical Statistics, London School of Hygiene & Tropical Medicine, London, UK
- ⁴Anne Rowling Regenerative Neurology Clinic, NHS Lothian, Edinburgh, UK
- ⁵University Hospital Southampton NHS Foundation Trust, Southampton, UK
- ⁶University Hospitals Coventry and Warwickshire NHS Trust, Coventry, UK
- ⁷Belfast City Hospital Health and Social Services Trust, Belfast, UK
- ⁸Oxford University Hospitals NHS Foundation Trust, Oxford, UK
- ⁹University Hospitals Dorset NHS Foundation Trust, Poole, UK
- ¹⁰University Hospitals Sussex NHS Foundation Trust, Brighton, UK
- ¹¹University Hospitals Plymouth NHS Trust, Plymouth, UK
- ¹²Bradford Teaching Hospitals NHS Foundation Trust, Bradford, UK
- ¹³University Hospital of Wales, Cardiff, UK
- ¹⁴University Hospitals of North Midlands NHS Trust, Stoke-on-Trent, UK
- ¹⁵Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK
- ¹⁶University of Cambridge, Cambridge, UK
- ¹⁷East Kent Hospitals University NHS Foundation Trust, Canterbury, UK
- ¹⁸Barking Havering and Redbridge University Hospitals NHS Trust, Romford, UK
- ¹⁹Royal Devon University Healthcare NHS Foundation Trust, Exeter, UK
- ²⁰The Walton Centre NHS Foundation Trust, Liverpool, UK
- ²¹Institute of Systems Molecular and Integrative Biology, University of Liverpool, Liverpool, UK
- ²²Norfolk and Norwich University Hospitals NHS Foundation Trust, Norwich, UK
- ²³Lancashire Teaching Hospitals NHS Foundation Trust, Preston, UK
- ²⁴Hull University Teaching Hospitals NHS Trust, Hull, UK
- ²⁵Department of Neurology, Salford Royal NHS Foundation Trust, Salford, UK
- ²⁶Department of Neurology, Lewisham and Greenwich NHS Trust, London, UK
- ²⁷Queen Elizabeth University Hospital, Glasgow, UK
- ²⁸Newcastle Upon Tyne Hospitals NHS Foundation Trust, Newcastle Upon Tyne, UK
- ²⁹Torbay and South Devon NHS Foundation Trust, Torquay, UK
- ³⁰Imperial College Healthcare NHS Trust, London, UK
- ³¹North Bristol NHS Trust, Bristol, UK
- ³²MS Society, London, UK
- ³³University of Exeter, Exeter, UK
- ³⁴Blizard Institute, Queen Mary University, London, UK
- ³⁵Institute of Ophthalmology, University College London, London, UK
- ³⁶Department of Primary Care and Population Health, University College London Research, London, UK
- ³⁷University of Leeds, Leeds, UK
- ³⁸Swansea Bay UHB, Swansea, UK
- ³⁹Nottingham University Hospitals NHS Trust, Nottingham, UK
- ⁴⁰Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK
- ⁴¹Clinical & Experimental Sciences, University of Southampton Faculty of Medicine, Southampton, UK
- ⁴²Division of Clinical and Surgical Sciences, University of Edinburgh, Edinburgh, UK
- ⁴³Centre for Neurosciences, Leeds General Infirmary, Leeds, UK

⁴⁴National Institute for Health Research, Biomedical Research Centre, University College London Hospitals, London, UK

X Rachel Merry @N/A, Seema Kalra @DrSeemaKalra, Gavin Giovannoni @gavingiovannoni and Helen L Ford @helenlouiseford

Acknowledgements Foremost we thank the participants in this trial for their tireless support, dedication and commitment. We thank all individuals who contributed to full, continuing and meaningful PPI. Our thanks to Dr Emma Gray and colleagues at the UK MS Society, Dr Bruce Bebo and colleagues at the National MS Society and to Prof Nick Freemantle and Ms Gemma Jones at the UCL CCTU. We also acknowledge the support of the independent members of the Trial Steering Committee (TSC): Dr Brendan Mclean, Prof Thomas Jaki, Dr Victoria Williams, Ms Trishna Vohra (to 2022) and Dr Caroline Sincock; and of the Independent Data Monitoring Committee (IDMC): Prof Graeme MacLennan, Prof Michael Hutchinson, Dr Heather Wilson (to 2022) and Dr Hugh Kearney. Finally, we thank the MS-STAT2 Investigators. We particularly here record the death in 2024, of our friend and colleague Dr Matt Craner.

Contributors JC, JN, CF, RH, MB, HLF, SChhetri, RN, SPavitt, EG, ST, OC, GG, JGanesalingam and AJT researched and wrote the original grant application. All are involved in the setup and running of the trial and contributed to the writing of the manuscript. JBlackstone represents the sponsor, developed the trial protocol and led the writing of the manuscript. JN, 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, FDA, AB, NJ, AC, AD, SAM, CW and MB 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 UCL CCTU 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. SJN and JBeveridge are PPI representatives and critically reviewed the manuscript. AShehu, GM, RG, MC, CH, JGreenwood, LF, JH, CS, NR, SK, SPluchino, SH, MM, TH, CY, ML, SChhetri, FA, DR, ES, PG, MD, AStraukiene, CR, OP, NE, BS, IG, SChandran, HLF and JC are site principal investigators and also contributed to the writing of the manuscript. JC is the chief investigator for the trial and contributed to the protocol and the manuscript. JC is the guarantor.

Funding This trial has been cofunded by the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) Programme—HTA Project: 15/57/143, the UK Multiple Sclerosis Society and the National Multiple Sclerosis Society in the USA.

Disclaimer The funders have no role in data collection, analysis, interpretation or writing of reports.

Competing interests JC has received support in the last 3 years from the Health Technology Assessment (HTA) Programme (National Institute for Health Research, NIHR), the UK MS Society, the US National MS Society and the Rosetrees Trust. He is supported in part by the NIHR University College London Hospitals (UCLH) Biomedical Research Centre, London, UK. He has been a local principal investigator for a trial in MS 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, Janssen, Lucid, Merck, NervGen, Novartis and Roche. OC declares being NIHR Research Professor (RP-2017-08-ST2-004); over the last 2 years, member of independent DSMB for Novartis; she gave a teaching talk in a Merck local symposium and 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, the Rosetree Trust, the US National MS Society and the NIHR-HTA. HLF has received honoraria for advisory boards and/or educational activities from Biogen, Merck, Novartis and Roche. HLF has research grant support from the NIHR Health Technology Assessment Programme and EME, UK MS Society and the Horne Family Charitable Trust. 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 that in the last 2 years he has received compensation for serving as a consultant or speaker or research support from Astoria Biologica, Aurinia Pharmaceuticals, Biogen, BMS-Celgene, GlaxoSmithKline, Janssens/J&J, Japanese Tobacco, Merck KGaA/EMD Serono, Moderna, Novartis, Sandoz, Sanofi, Roche/Genentech, Vir Biotechnology and Viracta. NJ is a principal investigator on commercial MS trials sponsored by Roche, Novartis and Biogen. He has received speakers honoraria from Merck and travel congress sponsorship from Novartis. MM has received travel support, speaker honoraria and consultation fees from Genzyme, Merck-Serono, Novartis, Roche, the MS Academy and the

Italian Multiple Sclerosis Foundation (FISM). RN attended paid advisory board for Novartis and Roche. SPavitt was MRC/National Institute for Health Research (NIHR)—Efficacy & Mechanism Evaluation Board Member from 2012–2018. SPulichino is founder, CSO and shareholder (>5%) of CITC and Chair of the Scientific Advisory Board at ReNeuron plc. CR declares research funding from Sanofi. DR declares consulting and/or speaker fees received from Biogen, Celgene, Janssen, MedDay, Merck, Novartis, Roche, Sanofi Genzyme and Teva. Additionally, research support paid to an institutional fund from Actelion, Biogen, GW Pharmaceuticals, Merck Serono, Mitsubishi, Novartis, Sanofi Genzyme, Teva and TG Therapeutics. AJT receives a fee from being Co-Chair, UCL-Eisai Steering Committee drug discovery collaboration; Member, National MS 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. He receives no fee from being: Chair (Scientific Ambassadors), ‘Stop MS’ Appeal Board, UK MS Society; Research & academic counsellor, Fundació Privada Cemcat; Ambassador, European Brain Council. AJT additionally holds a patent for the MSIS-29 Impact Scale.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution 4.0 Unported (CC BY 4.0) license, which permits others to copy, redistribute, remix, transform and build upon this work for any purpose, provided the original work is properly cited, a link to the licence is given, and indication of whether changes were made. See: <https://creativecommons.org/licenses/by/4.0/>.

ORCID iDs

James Blackstone <http://orcid.org/0000-0003-4335-5269>

Gavin Giovannoni <http://orcid.org/0000-0001-9995-1700>

Rachael Hunter <http://orcid.org/0000-0002-7447-8934>

Ian Galea <http://orcid.org/0000-0002-1268-5102>

Siddharthan Chandran <http://orcid.org/0000-0001-6827-1593>

Helen L Ford <http://orcid.org/0000-0002-4156-5046>

Jeremy Chataway <http://orcid.org/0000-0001-7286-6901>

REFERENCES

- Federation, M.I. Atlas of ms. 2023. Available: <https://www.atlasofms.org/map/global/epidemiology/number-of-people-with-ms> [Accessed 16 Feb 2024].
- Brownlee WJ, Altmann DR, Prados F, *et al*. Early imaging predictors of long-term outcomes in relapse-onset multiple sclerosis. *Brain (Bacau)* 2019;142:2276–87.
- Thompson AJ, Baranzini SE, Geurts J, *et al*. Multiple sclerosis. *Lancet* 2018;391:1622–36.
- Cree BAC, Gourraud P, Oksenberg JR, *et al*. Long-term evolution of multiple sclerosis disability in the treatment era. *Ann Neurol* 2016;80:499–510.
- Fambias A, Jokubaitis V, Horakova D, *et al*. Risk of secondary progressive multiple sclerosis: A longitudinal study. *Mult Scler* 2020;26:79–90.
- Vasanthaprasad V, Khurana V, Vadapalle S, *et al*. Systematic literature review and meta-analysis of the prevalence of secondary progressive multiple sclerosis in the USA, Europe, Canada, Australia, and Brazil. *BMC Neurol* 2022;22:301.
- Chataway J, Murphy N, Khurana V, *et al*. Secondary progressive multiple sclerosis: a systematic review of costs and health state utilities. *Curr Med Res Opin* 2021;37:995–1004.
- Kobelt G, Thompson A, Berg J, *et al*. New insights into the burden and costs of multiple sclerosis in Europe. *Mult Scler* 2017;23:1123–36.
- Hauser SL, Cree BAC. Treatment of Multiple Sclerosis: A Review. *Am J Med* 2020;133:1380–90.
- Chataway J, Williams T, Li V, *et al*. Clinical trials for progressive multiple sclerosis: progress, new lessons learned, and remaining challenges. *Lancet Neurol* 2024;23:277–301.
- Yong HYF, Yong VW. Mechanism-based criteria to improve therapeutic outcomes in progressive multiple sclerosis. *Nat Rev Neurol* 2022;18:40–55.
- Chataway J, Schuerer N, Alsanousi A, *et al*. Effect of high-dose simvastatin on brain atrophy and disability in secondary progressive multiple sclerosis (MS-STAT): a randomised, placebo-controlled, phase 2 trial. *Lancet* 2014;383:2213–21.
- Peng X, Jin J, Giri S, *et al*. Immunomodulatory effects of 3-hydroxy-3-methylglutaryl coenzyme-A reductase inhibitors, potential therapy for relapsing remitting multiple sclerosis. *J Neuroimmunol* 2006;178:130–9.
- Weber MS, Youssef S, Dunn SE, *et al*. Statins in the treatment of central nervous system autoimmune disease. *J Neuroimmunol* 2006;178:140–8.
- Youssef S, Stüve O, Patarroyo JC, *et al*. The HMG-CoA reductase inhibitor, atorvastatin, promotes a Th2 bias and reverses paralysis in central nervous system autoimmune disease. *Nature New Biol* 2002;420:78–84.
- Zamvil SS, Steinman L. Cholesterol-lowering statins possess anti-inflammatory activity that might be useful for treatment of MS. *Neurology (Ecricon)* 2002;59:970–1.
- Bagheri H, Ghasemi F, Barreto GE, *et al*. The effects of statins on microglial cells to protect against neurodegenerative disorders: A mechanistic review. *Biofactors* 2020;46:309–25.
- Pahan K, Sheikh FG, Namboodiri AM, *et al*. Lovastatin and phenylacetate inhibit the induction of nitric oxide synthase and cytokines in rat primary astrocytes, microglia, and macrophages. *J Clin Invest* 1997;100:2671–9.
- van der Most PJ, Dolga AM, Nijholt IM, *et al*. Statins: mechanisms of neuroprotection. *Prog Neurobiol* 2009;88:64–75.
- Endres M, Laufs U, Huang Z, *et al*. Stroke protection by 3-hydroxy-3-methylglutaryl (HMG)-CoA reductase inhibitors mediated by endothelial nitric oxide synthase. *Proc Natl Acad Sci U S A* 1998;95:8880–5.
- Giannopoulos S, Katsanos AH, Tsvigoulis G, *et al*. Statins and cerebral hemodynamics. *J Cereb Blood Flow Metab* 2012;32:1973–6.
- Xu G, Fitzgerald ME, Wen Z, *et al*. Atorvastatin therapy is associated with greater and faster cerebral hemodynamic response. *Brain Imaging Behav* 2008;2:94.
- Aviv RI, Francis PL, Tenenbein R, *et al*. Decreased frontal lobe gray matter perfusion in cognitively impaired patients with secondary progressive multiple sclerosis detected by the bookend technique. *AJNR Am J Neuroradiol* 2012;33:1779–85.
- De Keyser J, Steen C, Mostert JP, *et al*. Hypoperfusion of the cerebral white matter in multiple sclerosis: possible mechanisms and pathophysiological significance. *J Cereb Blood Flow Metab* 2008;28:1645–51.
- D’haeseleer M, Beelen R, Fierens Y, *et al*. Cerebral hypoperfusion in multiple sclerosis is reversible and mediated by endothelin-1. *Proc Natl Acad Sci U S A* 2013;110:5654–8.
- Lagana MM, Pelizzari L, Baglio F. Relationship between MRI perfusion and clinical severity in multiple sclerosis. *Neural Regen Res* 2020;15:646–52.
- Paling D, Thade Petersen E, Tozer DJ, *et al*. Cerebral arterial bolus arrival time is prolonged in multiple sclerosis and associated with disability. *J Cereb Blood Flow Metab* 2014;34:34–42.
- Cashion JM, Young KM, Sutherland BA. How does neurovascular unit dysfunction contribute to multiple sclerosis? *Neurobiol Dis* 2023;178:106028.
- D’haeseleer M, Cambon M, Vanopdenbosch L, *et al*. Vascular aspects of multiple sclerosis. *Lancet Neurol* 2011;10:657–66.
- Zierfuss B, Laroche C, Prat A. Blood-brain barrier dysfunction in multiple sclerosis: causes, consequences, and potential effects of therapies. *Lancet Neurol* 2024;23:95–109.
- Friese MA, Schattling B, Fugger L. Mechanisms of neurodegeneration and axonal dysfunction in multiple sclerosis. *Nat Rev Neurol* 2014;10:225–38.
- Wang Q, Yan J, Chen X, *et al*. Statins: multiple neuroprotective mechanisms in neurodegenerative diseases. *Exp Neurol* 2011;230:27–34.
- Mahad DH, Trapp BD, Lassmann H. Pathological mechanisms in progressive multiple sclerosis. *Lancet Neurol* 2015;14:183–93.
- Palladino R, Marrie RA, Majeed A, *et al*. Evaluating the Risk of Macrovascular Events and Mortality Among People With Multiple Sclerosis in England. *JAMA Neurol* 2020;77:820–8.

- 35 Williams T, John N, Calvi A, *et al.* Cardiovascular risk factors in secondary progressive multiple sclerosis: A cross-sectional analysis from the MS-STAT2 randomized controlled trial. *Eur J Neurol* 2023;30:2769–80.
- 36 Eshaghi A, Kievit RA, Prados F, *et al.* Applying causal models to explore the mechanism of action of simvastatin in progressive multiple sclerosis. *Proc Natl Acad Sci U S A* 2019;116:11020–7.
- 37 Almramhi MM, Finan C, Storm CS, *et al.* Exploring the Role of Plasma Lipids and Statin Interventions on Multiple Sclerosis Risk and Severity: A Mendelian Randomization Study. *Neurology (Echronicon)* 2023;101:e1729–40.
- 38 Greenwood J, Steinman L, Zamvil SS. Statin therapy and autoimmune disease: from protein prenylation to immunomodulation. *Nat Rev Immunol* 2006;6:358–70.
- 39 Greenwood J, Walters CE, Pryce G, *et al.* Lovastatin inhibits brain endothelial cell Rho-mediated lymphocyte migration and attenuates experimental autoimmune encephalomyelitis. *FASEB J* 2003;17:905–7.
- 40 EMA. CHMP guideline on clinical investigation of medicinal products for the treatment of multiple sclerosis. 2015.
- 41 Polman CH, Reingold SC, Banwell B, *et al.* Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. *Ann Neurol* 2011;69:292–302.
- 42 Polman CH, Reingold SC, Edan G, *et al.* Diagnostic criteria for multiple sclerosis: 2005 revisions to the “McDonald Criteria.” *Ann Neurol* 2005;58:840–6.
- 43 Thompson AJ, Banwell BL, Barkhof F, *et al.* Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *Lancet Neurol* 2018;17:162–73.
- 44 Lublin FD, Reingold SC. Defining the clinical course of multiple sclerosis: results of an international survey. National Multiple Sclerosis Society (USA) Advisory Committee on Clinical Trials of New Agents in Multiple Sclerosis. *Neurol (Echronicon)* 1996;46:907–11.
- 45 Lublin FD, Reingold SC, Cohen JA, *et al.* Defining the clinical course of multiple sclerosis: the 2013 revisions. *Neurology (Echronicon)* 2014;83:278–86.
- 46 Lechner-Scott J, Kappos L, Hofman M, *et al.* Can the Expanded Disability Status Scale be assessed by telephone? *Mult Scler* 2003;9:154–9.
- 47 Ontaneda D, Fox RJ, Chataway J. Clinical trials in progressive multiple sclerosis: lessons learned and future perspectives. *Lancet Neurol* 2015;14:208–23.
- 48 Andersen O, Elovaara I, Färkkilä M, *et al.* Multicentre, randomised, double blind, placebo controlled, phase III study of weekly, low dose, subcutaneous interferon beta-1a in secondary progressive multiple sclerosis. *J Neurol Neurosurg Psychiatry* 2004;75:706–10.
- 49 Panitch H, Miller A, Paty D, *et al.* Interferon beta-1b in secondary progressive MS: results from a 3-year controlled study. *Neurology (Echronicon)* 2004;63:1788–95.
- 50 Ball S, Vickery J, Hobart J, *et al.* The Cannabinoid Use in Progressive Inflammatory brain Disease (CUPID) trial: a randomised double-blind placebo-controlled parallel-group multicentre trial and economic evaluation of cannabinoids to slow progression in multiple sclerosis. *Health Technol Assess* 2015;19:vii–viii, .
- 51 Coffman CJ, Edelman D, Woolson RF. To condition or not condition? Analysing “change” in longitudinal randomised controlled trials. *BMJ Open* 2016;6:e013096.
- 52 Kuspinar A, Mayo NE. A review of the psychometric properties of generic utility measures in multiple sclerosis. *Pharmacoeconomics* 2014;32:759–73.
- 53 Hobart J, Cano S. Improving the evaluation of therapeutic interventions in multiple sclerosis: the role of new psychometric methods. *Health Technol Assess* 2009;13:iii, .
- 54 Hawton A, Green C, Telford C, *et al.* Using the Multiple Sclerosis Impact Scale to estimate health state utility values: mapping from the MSIS-29, version 2, to the EQ-5D and the SF-6D. *V H* 2012;15:1084–91.
- 55 Hunter RM, Baio G, Butt T, *et al.* An educational review of the statistical issues in analysing utility data for cost-utility analysis. *Pharmacoeconomics* 2015;33:355–66.
- 56 NICE. NICE health technology evaluations: the manual (PMG36), 2022. Available: <https://www.nice.org.uk/process/pmg36/chapter/economic-evaluation#the-reference-case-framework> [Accessed 15 Feb 2024].

APPENDIX 1: Protocol amendments table

Protocol Version	Protocol Date	Summary of Changes
1.0	1- Aug- 2017	N/A
2.0	24-Jan-2018	<ol style="list-style-type: none"> 1. Addition of a new exclusion criteria – Patients with rare hereditary problems of galactose intolerance, the lapp lactase deficiency or glucose-galactose malabsorption may experience a serious reaction to use of simvastatin as each 40mg film-coated tablet contains 116.4 mg lactose per film-coated tablet. Exclusion criteria to be amended to ensure patients with lactose intolerance as a result of rare hereditary problems of galactose intolerance, the lapp lactase deficiency or glucose-galactose malabsorption are not enrolled to the trial 2. Inclusion of trial identifiers <ul style="list-style-type: none"> - ClinicalTrials.gov unique identifier - Clinical Trial Authorisation (CTA) number 3. Use of two new questionnaires at all participating sites <ol style="list-style-type: none"> a. Modified Fatigue Index Scale – 21 (MFIS-21) b. Chalder Fatigue Questionnaire (CFQ) 4. Addition of three sub-studies at participating site(s) only <ul style="list-style-type: none"> - MRI sub-study (Appendix 1) - Biomarker sub-study (Appendix 2) - OCT sub-study (Appendix 3) 5. Recruitment of healthy blood donors for the biomarker sub-study 6. Change from ABILHAND-56 to ABILHAND-23 7. Section 7.5.1 has been revised to outline process of obtaining consent from sub-study participants 8. SAE form to be sent to trial team via secure portal/encrypted 9. Change in wording – Oversight group changed from Independent Data and Monitoring Committee (IDMC) to Data Monitoring and Ethics Committee (IDMC) in line with funder (NIHR) terminology 10. Editing of section 6.11.3.4: Procedures following notification of pregnancy 11. Addition of section 6.11.3.4.2 Notification by male participants in the event of partner becoming pregnant 12. Addition of new terms to Glossary (section 4) 13. Minor edits and formatting throughout the protocol
3.0	02-Aug-2018	<ol style="list-style-type: none"> 1. New logo for UCL CCTU (front page) 2. Addition of reference to EU General Data Protection (GDPR) 2016 in section 1.1, 6.10 3. Inclusion criteria edited to remove: <ul style="list-style-type: none"> - that patients must have entered the secondary progressive stage ‘at randomisation’ - inclusion criteria for being male or female 4. Date of first enrolment amended to May 2018 (structured summary section 1.3) 5. Addition of CSRI form as a secondary outcome measure (structured summary section 1.3) 6. List of sub-studies added to structured summary (section 1.3) 7. Protocol contributors (section 1.4.1), Trial sponsor and funders (section 1.4.2), Trial team (section 1.4.3), Trial Management Group (section 1.4.4), Trial Steering Committee (section 1.4.5), Independent Data Monitoring Committee (section 1.4.6), and Recruitment Management Group (section 1.4.6) edited due to staff changes and to add clarity and consistency. 8. References to DMEC changed to IDMC throughout 9. Inclusion criteria (section 1.3, 6.3.1.2 and 6.5.1) updated to remove reference to screening EDSS 10. Addition of new terms to Abbreviations (section 3)

Protocol Version	Protocol Date	Summary of Changes
		<ol style="list-style-type: none"> 11. Addition of new terms to Glossary (section 4) 12. Secondary objectives (section 5.2.2.2) updated for clarity, to add CSRI form, be clear which outcomes relate to Health Economics, and to remove SF-36 and ABILHAND-23 13. Visit numbers edited to refer to month numbers only (week numbers removed) 14. Eligibility criteria for individuals performing the interventions clarified and moved to section 6.5.5.3 15. Co-enrolment guidance (section 6.3.1.5) clarified 16. Blood samples taken during screening procedures (section 6.3.1.6) clarified 17. Clarification added that if screening blood tests are clinically significant these should be repeated prior to the baseline visit (section 6.3.1.6) 18. Clarification around re-screening patients under new patient identification numbers added (section 6.3.1.6) 19. Drug referred to as 'trial medication' consistently 20. Clarification around additional visit 11 added (section 6.4.2 and figure 1) 21. Accountability (section 6.4.5) updated to state patients should return all unused trial medication at each visit, and that destruction can occur as per standard local policy 22. Compliance and adherence (section 6.4.6) updated to clarify that the diary card will record doses trial medication taken since the last visit 23. Concomitant care (section 6.4.7) updated for clarity in relation to statins and DMDs 24. Contraindicated medications (section 6.4.8) updated regarding re-starting trial medication after taking a contraindicated medication for a short period of time 25. Overdose (section 6.4.9) updated to state that patients who overdose should discontinue trial medication but remain in follow up and not be withdrawn 26. Protocol treatment discontinuation (section 6.4.10) updated to state that patients should remain in follow up unless they specifically withdraw consent to do so 27. Primary outcome (section 6.5.1) updated to clarify when the EDSS should be done by a treating or assessing clinician 28. SLCVA, CVLT-II, BVMT-R (section 6.5.2.1) guidance updated for clarity and to specify which subsets of the CVLT-II and BVMT-R are being completed as part of BICAMS 29. Relapse assessment guidance (section 6.5.1) updated to be clear that grade 3 relapses should be reported as an SAE 30. Participant timeline (section 6.6) updated to increase the number of timepoints the 9HPT and T25FW completed at 31. Participant timeline (section 6.6) updated to reduce the number of timepoints the SLVCA, mRS, MSIS-29v2, MSWS-12v2, EQ-5D-5L and Lipid profile completed at, and to remove the SF-36 32. Loss to follow-up (section 6.6.3) updated to include methods to attempt to contact patients before considered lost to follow up, and the use of telephone assessment EDSS and posted patient reported outcome measure for patients that are unable to attend clinic 33. Participant timeline (section 6.6) updated to reduce the number of timepoints bloods are taken for the biomarkers sub-study 34. Additional footnotes added to participant timeline (section 6.6) for clarity 35. Participant timeline (section 6.6) updated to move ABILHAND-23 to sub-study section as now being using only at the lead site (UCLH) as a sub-study 36. Participant timeline (section 6.6) additional footnote added regarding timing of baseline MRI scan for MRI sub-study 37. Early stopping of follow up (section 6.6.1) updated in regards to intention-to-treat 38. Participant transfers (section 6.6.2) updated in regards to responsibility for resolution of data queries 39. Loss to follow-up (section 6.6.3) updated to clarify procedures for preventing loss to follow up 40. Recruitment (section 6.81) updated to specify when PIS should be provided to potentially interested patients

Protocol Version	Protocol Date	Summary of Changes
		<p>41. Figure 2 updated with a more accurate map of expected sites</p> <p>42. Assignment of intervention (section 6.9) updated to clarify that the patient identification number will be the screening number, and the patient will be randomised under this number. References to drug identification codes replaced with 'kit codes'</p> <p>43. New section 6.9.4 added for unblinding following trial closure</p> <p>44. Data collection methods (section 6.10.1) updated regarding training required for EDSS as the primary outcome measure.</p> <p>45. Data collection methods (section 6.10.1) updated clarifying which documentation is considered as source documentation</p> <p>46. Non-adherence and non-retention (section 6.10.3) updated in regards to how compliance is assessed</p> <p>47. Statistical analysis plan (section 6.10.4.1) updated to clarify that only the IDMC will see the result of interim unblinded analyses</p> <p>48. Analysis population and missing data (section 6.10.5) updated to clarify that compliance will be assessed on reported missed doses</p> <p>49. Health economics (section 6.10.6) sections numbered for clarity</p> <p>50. Health Economics (section 6.10.6.2) updated to remove that an application will be made for Hospital Episode Statistics</p> <p>51. Timing of interim analyses (section 6.11) updated due to annually</p> <p>52. Data monitoring for harm (section 6.11.3) updated in regard to requirements for reporting AEs solely related to MS</p> <p>53. Other notifiable AEs (section 6.11.3.3) updated to include reporting pregnancies for female partners of male participants</p> <p>54. Notification of SAEs by investigators to CCTU (section 6.11.3.6.1) updated to state month and year of birth will be collected not full date of birth</p> <p>55. CCTU responsibilities for clinical review of SAEs (section 6.11.3.6.2) clarified</p> <p>56. Confidentiality (section 7.6) updated to provide additional information</p> <p>57. Appendix 1 MRI sub-study, Appendix 2 Biomarkers sub-study, Appendix 3 OCT sub-study have had eligibility criteria added</p> <p>58. Appendix 1 MRI sub-study eligibility (section 1) state that patients that cannot tolerate gadolinium can still participate without gadolinium</p> <p>59. Appendix 1 MRI sub-study the secondary outcomes (section 5.1.2) have been updated to correct the minimisation variables</p> <p>60. Appendix 1 MRI sub-study secondary outcomes (section 7.1.2) clarified</p> <p>61. Appendix 2 Biomarkers sub-study data collection for healthy donor (section 1.3) updated to state initials not name will be collected</p> <p>62. Appendix 2 Biomarkers sub-study Aims (section 2) updated to specify exactly what samples will be tested</p> <p>63. Appendix 2 Biomarkers sub-study objectives (section 5) clarified</p> <p>64. Appendix 2 Biomarkers sub-study outcomes (section 6) updated to clarify outcomes and include additional exploratory outcome</p> <p>65. Appendix 4 ABILHAND-23 sub-study added</p>
4.0	22-Jul-2019	<p>1. Exclusion criteria updated to exclude patients taking elbasvir, grazoprevir and recent cladribine (structured summary section 1.3, section 6.3.1.3)</p> <p>2. Exclusion criteria updated to state dimethyl fumarate instead of just fumarate (structured summary section 1.3, section 6.3.1.3)</p> <p>3. Structured summary (section 1.3) updated primary outcome should be change in EDSS in comparison to baseline visit (not screening visit)</p> <p>4. Creatinine kinase corrected to creatine kinase throughout</p> <p>5. Laboratory abnormalities (section 6.4.4.1) updated to include further information about myopathy</p>

Protocol Version	Protocol Date	Summary of Changes
		<ol style="list-style-type: none"> 6. Laboratory abnormalities (section 6.4.4.1) updated to provide greater clarity on the dose modification strategy due to AEs and other reasons. 7. Contraindicated medications (section 6.4.8) updated to include elbasvir and grazoprevir 8. Trial closure (section 6.6.4) definition of end of trial updated 9. SLCVA guidance (section 6.5.2.1) updated to state that the SLVCA should only be tested binocularly. 10. Participant timeline (section 6.6) updated to remove the FAB. The FAB will only be completed at baseline and visit 10 at UCLH as a separate sub-study 11. Participant timeline (section 6.6) footnote B edited to state that safety bloods do not require fasting and to remove potassium and sodium for safety bloods test except at screening 12. Map (section 6.8.1) updated to show currently open sites 13. Clarification that only AEs which are both non-serious AND can be attributed solely to the progression of the patient's SPMS condition can be excluded from reporting (section 6.11.3.2). 14. Section 6.11.3.5.2 updated from CTCAE V4 to CTCAE V5 15. Section 6.11.3.5.4 updated in relation to sponsor assessing expectedness for SAEs 16. Section 6.11.3.6.1 updated to remove investigator assessing expectedness for SAEs 17. Section 6.11.3.5.2 updated in relation to sponsor assessing expectedness for SAEs 18. References corrected for minor duplication and entered into Endnote system. 19. Appendix 2 Biomarkers sub-study aims (section 2) updated, frozen serum and plasma samples will be stored to allow future analysis of novel biomarkers. Order of paragraphs changed to improve fluidity of reading. 20. Appendix 3 OCT sub-study updated to include Sloan Low Contrast (100/2.5/1.25%) assessment for OS/OD (removed from main study for other sites). 21. Appendix 5 added for FAB sub-study
5.0	23-Mar-2020	<ol style="list-style-type: none"> 1. Clarification in Section 6.4.3.1 that safety blood testing will be performed at the following visits: <ul style="list-style-type: none"> - Visit 3 (Month 1) to evaluate patient tolerance of low (40mg) IMP dose - Visit 4 (Month 3) to evaluate patient tolerance of high (80mg) IMP dose - Visit 5 (Month 6) to Visit 10 (Month 36) at least annually <p>Where a patient cannot attend clinic/GP to receive safety blood evaluation of tolerance of high dose at Visit 4 (month 3), they should be de-escalated to low (40mg) dose, which is already known to be tolerated, and re-challenged subsequently where no clinical reason not to do so.</p> <p>Once a patient is established on high (80mg) dose, it is appropriate for patients to have safety blood testing at least annually from this point. Where clinical need is indicated, safety blood testing may be more frequent (e.g. six-monthly).</p> <p>Patients will not have additional IMP dispensed to them where it has been ≥12 months since last evaluation of safety bloods.</p>
6.0	11-Aug-2020	<ol style="list-style-type: none"> 1. Exclusion criteria (section 1.3 and section 6.3.1.3) updated to clarify minimum acceptable period since MS relapse 2. Exclusion criteria (section 1.3 and section 6.3.1.3) updated to exclude patients taking Ticagrelor and Daptomycin 3. Laboratory abnormalities (section 6.4.4.1) updated to include information about concomitant medications Ticagrelor and Daptomycin.

Protocol Version	Protocol Date	Summary of Changes
		<ol style="list-style-type: none"> 4. Dose modification guidance for re-challenging IMP updated (section 6.4.4.2 and 6.4.4.3) 5. Concomitant medications Ticagrelor and Daptomycin added to contraindicated medications (section 6.4.8). 6. Participant timeline (section 6.6) updated to allow, under exceptional circumstances (i.e. due to COVID-19) the following: <ul style="list-style-type: none"> - Screening (visit 1) and baseline (visit 2) can be combined - Month 1 (visit 3) can be remote 7. Loss to follow-up (section 6.6.3) updated to include categories of trial participation, and related guidance 8. Figure 2: Map of expected MS-STAT2 sites (section 6.8.1) updated
7.0	17-Feb-2021	<ol style="list-style-type: none"> 1. Structured summary (section 1.3) updated to reflect changes in the main body of the protocol. 2. Details of CCTU trial team, MS Society staff and PPI representation updated (section 1.4). 3. Trial diagram updated to include additional visits for certain patients (section 2). 4. Updated of abbreviations to include LPLV ('last patient last visit') (section 3). 5. Glossary updated to define meaning of last patient last visit (section 4). 6. Aim of trial redefined to determine whether rate of disability progression can be slowed over the duration of the treatment period, rather than 3 years as previously (section 5.2.1) 7. Primary objective updated to note for those patients requiring a final visit following Visit 10 specifically to confirm their progression event but who lack 6 months until LPLV, can have their visit 3-6 months after Visit 10 should time until LPLV allow (section 5.2.2.1). 8. Trial design section updated to allow a series of additional 6-monthly visits for those patients who have not had a confirmed progression event by their Visit 10 (36M). There will be between 1-3 additional visits, dependant on time remaining until LPLV date (section 5.3). 9. Treatment schedule updated to include provision that patients are requested to attend additional visits after Visit 10 will remain on IMP between these visits (section 6.4.2). 10. Schematic showing drug regimen updated (section 6.3). 11. Primary outcome updated to address previous error by noting EDSS scores at follow-up visits will be evaluated against baseline EDSS (not screening EDSS). Wording also updated to confirm where patients have less than 6 months until LPLV but need a confirmatory final visit for an initial progression can do so at 3-6 months from Visit 10, where time until LPLV allows (section 6.5.1). 12. Secondary outcome analysis updated to focus on proportion of progression events rather than time to progression (section 6.5.2). 13. Participant timeline updated to allow for additional visits beyond 36 months for those patients yet to have a confirmed progression event (section 6.6). 14. New section added to explain process of determining whether patients reaching Visit 10 (36M) will be asked to attend additional visits or end their trial pathway at the Visit 10 timepoint (section 6.6.2). 15. Sample size updated to explain the decision to reduce the sample size from 1,180 to 1,050 patients – including the potential for reducing further to 950 patients owing to COVID-19 impacts on recruitment. The implications for power on primary outcome are also addressed (section 6.7) 16. Statistical methods (outcomes) revised on when the primary outcome censor point will occur (final patient visit where a confirmed progression could occur, rather than 36 months post-baseline). Also proportion rather than time to disability will be used

Protocol Version	Protocol Date	Summary of Changes
		<p>in the secondary outcome analyses, using a mixed effect logistic regression approach, rather than time to event analysis (section 6.10.4.2)</p> <p>17. Additional analyses – adjusted has been updated to add the wording ‘or inclusion as a random effect’ in relation to centre variability (section 6.10.4.3)</p> <p>18. Analysis population updated to clarify that patient adherence will be assessed until their final visit rather than 3 years (section 6.10.5).</p>
V8.0	26-Feb-2024	<ol style="list-style-type: none"> 1. Structured summary updated to reflect changes throughout the main body of the protocol (section 1.3) 2. Staffing names, roles and affiliations updated (section 1.4) 3. Background/rationale updated to reflect current UK/global prevalence data, alongside updated patient costs estimates. Additionally, the limited introduction of Siponimod in the UK context is noted. Finally, recent research exploring the potential mechanisms of action for statins are provided. 4. The primary objective is updated to remove the option that participants with initial disease progression at v10 can have a confirmatory visit 3-6 months later. Instead, all visits are treated equally in this respect (section 5.2.2.1). 5. The secondary objectives have been given additional granularity on analysis approach (section 5.2.2.1). 6. In line with the update to the primary objective, wording supporting a confirmatory visit 3-6 months after an initial progression at visit 10 is removed (sections 5.3, 6.4.2, 6.4.3, and 6.5.1, and 6.6 Footnote). 7. The expectation that in-person visits should take place at Baseline and Visit 10 is clarified (section 6.6 footnote). 8. Further detail is provided around planned statistical subgroup analyses in light of the COVID-19 pandemic in 2020-21 (section 6.10.4.1). 9. Correction of a typo that omitted in error the word 'confirmed' in relation to the composite outcome definition in Statistical Methods (section 6.10.4.2).

Supplementary Table. Schedule of assessments

Clinic visit number	VISIT 1	VISIT 2	VISIT 3	VISIT 4	VISIT 5	VISIT 6	VISIT 7	VISIT 8	VISIT 9	VISIT 10	VISIT 11*	VISIT 12*	VISIT 13*
Month	SCREENING	Month 0 BASELINE	Month 1	Month 3 TELEPHONE	Month 6	Month 12	Month 18	Month 24	Month 30	Month 36	Month 42	Month 48	Month 54
Protocol window		(≤1m from screening)	(+/-1 week)	(+/-1 week)	(+/- 2 weeks)	(+/- 2 weeks)	(+/-2 weeks)	(+/-2 weeks)	(+/-2 weeks)	(+/-2 weeks)	(+/-2 weeks)	(+/-2 weeks)	(+/-2 weeks)
Informed consent	X												
Inclusion/exclusion criteria review	X	X											
Demography, Review of medical & MS history	X												
EDSS – Treating clinician	X												
Physical examination	X		X		X	X	X	X	X	X	X	X	X
Vital signs	X		X		X	X	X	X	X				
Urine pregnancy test	X	X											
Safety bloods	X	X	X	X	X	X	X	X	X	X	X	X	X
Lipid profile, Thyroid function	X												
Compliance assessment			X	X	X	X	X	X	X	X	X	X	X
Relapse assessment (count & grade)	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events		X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X
Randomisation		X											
Dispense trial medication		X	X		X	X	X	X	X	X	X	X	
Trial medication - dose escalation			X										
Clinician reported outcome measures													
EDSS – Independent Assessing clinician		X			X	X	X	X	X	X	X	X	X
9HPT, T25FW		X			X	X	X	X	X	X	X	X	X
SDMT: SLCVA, mRS		X				X		X		X			
CVLT-II, BVM-T-R		X								X			
Patient reported outcome measures													
MSIS-29v2, MSWS-12v2, MFIS-21, CFQ		X				X		X		X			
CSRI, EQ-5D 5L		X			X	X	X	X	X	X			

* Visits 11-13 form an 'extension' period follow-up for participants who do not have CDP on the EDSS Step score on/by Visit 10.