Multiple sclerosis (MS) is a lifelong condition which affects the central nervous system (the brain and spinal cord). It is estimated that 120,000 people in the UK have MS, which is commonly diagnosed in people during their 20s and 30s.

There are three main types of MS: relapsing remitting MS, primary progressive MS and secondary progressive MS. Secondary progressive multiple sclerosis (SPMS) is a stage of MS which follows the relapsing remitting stage for many people with the condition. With SPMS, disability gets steadily worse and patients are no longer likely to have relapses - where symptoms deteriorate but then improve. The SPMS stage accounts for most disability in people with MS. Currently there are few effective treatments that slow or stop the progression of disability associated with SPMS.

The MS-STAT study assessed whether simvastatin - an existing drug already widely used for treatment of vascular disease and raised cholesterol (with an excellent safety profile) - could be repurposed to make an effective drug for treating SPMS, due to its potential immunomodulatory and neuroprotective properties.

**Summary**

A double-blind, controlled trial was undertaken by a research team led by chief investigator Dr Jeremy Chataway, between January 2008 and November 2011. As part of the phase 2 trial, 140 participants aged 18–65 years with SPMS were randomly assigned to receive either high dose simvastatin (80mg), or placebo. Participants in the trial all had increasing disability over the preceding two years caused by steady progression of SPMS, rather than relapse.

Information about treatment allocation – who was receiving simvastatin vs placebo - was masked to patients, treating physicians, and outcome assessors participating in the study, eliminating the potential for bias.

The primary outcome tested as part of the trial was the annualised rate of brain shrinkage – known as whole-brain atrophy - measured by serial volumetric MRI at 0, 1 and 2 years. Patient reported outcomes were also assessed through instruments such as the Multiple Sclerosis Impact Scale-29 (MSIS-29) and the 36-Item Short Form Health Survey (SF-36).

A secondary analyses of MS-STAT (published in 2017) also assessed the results of a sub-study, which investigated comprehensive longitudinal cognitive, neuropsychiatric, and health related quality of life measures - which at the time of publication was the largest SPMS cohort to undergo such a series of assessments over time.

**Key features**

- Three year study between 2008 – 2011
- 140 participants recruited, aged 18–65 years with secondary progressive multiple sclerosis
- Existing cholesterol drug, simvastatin, repurposed for SPMS treatment through high dose regimen
- One of the first drug trials to demonstrate an effect on MS progression
- Three sites across London and South East England: St Mary’s, Imperial College London (the study’s sponsor); Chalfont St Peter, University College London; and Brighton and Sussex University Hospitals NHS Trust
- Chief investigator: Dr Jeremy Chataway, FRCP Consultant Neurologist/Reader in Neurology, UCL Institute of Neurology

**NIHR involvement & funding:**

- The study was accepted on to the NIHR Clinical Research Network Portfolio of Studies in 2008.
- It was part funded by UK National Institute of Health Research (NIHR) University College London Hospitals/UCL Biomedical Research Centres funding scheme, along with The Moulton Foundation, Berkeley Foundation, the Multiple Sclerosis Trials Collaboration, Rosetrees Trust and a personal contribution from A Pidgley.
Outcomes and findings

The 24 month MS-STAT trial showed that high does simvastatin significantly reduced the rate of whole brain atrophy (0.288% per year [SD 0.521]) compared to those the placebo group (0.584% per year [0.498]). The adjusted difference in atrophy rate between groups was −0.254% per year (95% CI −0.422 to −0.087; p=0.003); which is a 43% reduction in the annualised rate of brain atrophy.

- The study also demonstrated effects on clinician and patient observed outcome measures.
- High dose simvastatin was also well tolerated by participants, with no differences between the placebo and simvastatin groups in terms of serious adverse events (14 [20%] vs nine [13%]).
- The findings from this phase 2 study provide evidence that the use of simvastatin for treatment of SPMS patients may be both effective and safe. The effect on brain atrophy rate is positive, given that longitudinal studies have shown a relation between atrophy progression and disability.
- A secondary analysis of MS-STAT which described the results of the sub-study looking at cognitive, neuropsychiatric, and health-related quality-of-life outcome measures (published in The Lancet Neurology, June 2017) also evidenced a positive effect of simvastatin on frontal lobe function and a physical quality-of-life measure - adding to the previous findings.

Impact

Dr Jeremy Chataway, FRCP Consultant Neurologist and chief investigator of the study said: “MS-STAT was one of the first trials to demonstrate a positive effect on MS progression for any type of drug.

“The use of simvastatin as a treatment for SPMS potentially yields considerable financial savings for the NHS – with the cheap, repurposed drug costing around 8p per tablet – compared with existing treatments for MS progression which come with significant cost, despite limited efficacy against SPMS.”

The results of the study paved the way for MS-STAT2 - a phase 3 clinical trial assessing whether simvastatin can slow disability progression over a three-year period. It involves a much larger study group of 1,180 participants – at over 30 trial centres across the UK, and will take six years to complete.

The research team, which is being supported by the NIHR Clinical Research Network, will measure MS progression using a primary outcome of the Expanded Disability Status Scale (EDSS) as well as many other clinician and patient related measures.

“Since we published MS-STAT, there has been significant global interest in the use of simvastatin for progressive MS and the study has been widely reported.”

“Currently there are very little opportunities to slow or stop the accumulation of disability associated with MS. My hope is that if we can demonstrate a positive effect against the much larger cohort involved in MS-STAT2 – then simvastatin will be part of the treatment opportunity for secondary progressive MS.”

“It is essential in these difficult areas that trials are available for people and that they take part in these trials. MS-STAT and the work and funding behind it fulfils that mission exactly.”

Dr Jeremy Chataway, FRCP Consultant Neurologist and Chief Investigator

Key publications:

- MS-STAT2 (phase 3 clinical trial) information: http://bit.ly/2Drok5D