Introduction:

There remains an unmet need in the treatment of people with non-active progressive multiple sclerosis (PMS). Metformin has been put forward as a highly promising repurposed drug in PMS due to its potential for remyelination and neuroprotection.

Objectives/Aims:

To evaluate whether metformin, as add-on treatment, in patients with progressive non-active MS is superior to placebo in delaying disease progression.

Methods:

The study is designed as a multicentre two-arm, 1:1 randomised, triple-blind, placebo-controlled clinical trial, conducted in five clinical trial centres in Flanders. The eligibility criteria include: age 18-70 years (inclusive); progressive non-active MS (defined as no relapses, no new T2 lesions on brain MRI and progression independent of relapse activity in the past year); Expanded Disability Status Score (EDSS) 2-6.5 (inclusive); stable disease modifying treatment regimen in the past year. Diabetes mellitus is an exclusion criterion. A total of 120 patients will be enrolled and will have a screening visit with assessment of baseline MRI, clinical tests,
questionnaires, and a safety laboratory assessment. After randomisation at baseline, patients will receive treatment (metformin versus placebo) and follow-up for a period of 96 weeks. Four onsite visits will alternate with four remote telephone visits.

**Results:**

The primary outcome will be the change in walking speed, as measured by the Timed 25-Foot Walking Test (T25FWT), from baseline to 96 weeks of treatment, as compared between both treatment groups (metformin versus placebo). Secondary outcome measures will include change in general disability (EDSS score), information processing speed (Symbol Digit Modalities Test) and hand function (9-hole Peg test). To support the clinical effects, neurodegeneration and remyelination will be measured using magnetic resonance imaging brain volumetry and diffusion metrics. As exploratory outcomes, paramagnetic rim lesions, additional clinical tests and cost-effectiveness will be assessed. Safety monitoring is done by laboratory assessment and reporting of (serious) adverse events.

**Conclusion:**

This clinical trial aims to demonstrate the clinical benefit of metformin in PMS patients and will provide new insights into the treatment of PMS.

**Disclosures:**

AD received conference travel support from Biogen and research funding from Belgian Charcot Foundation. VP has received honoraria and travel and research grants from Almirall, Biogen, Medtronic, Merck, Novartis, Roche, Sanofi-Genzyme, Teva Pharmaceuticals. GL and/or his institution received speaker honoraria, advisory board fees, research support, or conference travel support from Biogen, BMS/Celgene, Merck Healthcare KGaA (Darmstadt, Germany), Sanofi, Teva, Roche, and Novartis. BW received honoraria for acting as a member of Scientific Advisory Boards/Consultancy for Almirall, Biogen, Celgene/BMS, Merck, Janssen, Novartis, Roche, Sandoz, Sanofi-Genzyme and speaker honoraria and travel support from Biogen, Celgene/BMS, Merck, Novartis, Roche, Sanofi-Genzyme; research and/or patient support grants from Biogen, Janssen, Merck, Sanofi-Genzyme, Roche. Honoraria and grants were paid to UZA/UZA Foundation. Further, B.W. received research funding from FWO-TBM, Belgian Charcot Foundation, Start2Cure Foundation, Queen Elisabeth Medical Foundation for Neurosciences and the National MS Society USA. All other authors report no potential conflicts. MACSIMISE BRAIN is funded by Research Foundation Flanders (FWO), Start2Cure Foundation, National Multiple Sclerosis Society USA and Belgian Charcot Foundation.