BMJ Open

Measuring and predicting the effect of remyelinating therapy in multiple sclerosis: a randomised controlled trial protocol (RESTORE)

Sam Hof ,[1] Laurentius J van Rijn,[2,3] Bernard M J Uitdehaag,[1] Jenny A Nij Bijvank,[1,2] Axel Petzold[1,4]

To cite: Hof S, van Rijn LJ, Uitdehaag BMJ, *et al*. Measuring and predicting the effect of remyelinating therapy in multiple sclerosis: a randomised controlled trial protocol (RESTORE). *BMJ Open* 2024;**14**:e076651. doi:10.1136/bmjopen-2023-076651

► Prepublication history for this paper is available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2023-076651).

Received 13 June 2023
Accepted 09 January 2024

[1]MS Center and Neuro-ophthalmology Expertise Center Amsterdam, Amsterdam UMC Location VUmc, Amsterdam, Noord-Holland, The Netherlands
[2]Ophthalmology, Amsterdam UMC Location VUmc, Amsterdam, Noord-Holland, The Netherlands
[3]Opthalmology, Onze Lieve Vrouwe Hospital, Amsterdam, Noord-Holland, The Netherlands
[4]Moorfields Eye Hospital NHS Foundation Trust, London, UK

Correspondence to
Sam Hof;
s.n.hof@amsterdamumc.nl

ABSTRACT

Introduction Remyelination failure hampers symptomatic recovery in multiple sclerosis (MS), underlining the importance of developing remyelinating therapies. Optic neuritis is currently the most established method of measuring remyelination in MS trials. Complementary more generalisable methods of measuring remyelination are required to confirm treatment efficacy. Measuring internuclear ophthalmoplegia (INO) with infrared oculography provides such a method. Moreover, this method can be expanded with a test for selecting likely treatment responders by using fampridine. The aim of this trial is to investigate the (long-term) remyelinating effects of clemastine fumarate in patients with MS and INO and to evaluate if treatment response can be predicted using fampridine.

Methods and analysis RESTORE is a single-centre double-blind randomised placebo-controlled trial of clemastine fumarate versus placebo. Prior to clemastine treatment improvement in oculographic features of INO after a single 10 mg dose of fampridine is measured in all participants and used to predict the treatment response to clemastine. Eighty individuals with MS and INO will be 1:1 randomised to 4 mg of clemastine fumarate two times a day for 6 months or equivalent placebo. Our primary outcome is improvement in the Versional Dysconjugacy Index-area under the curve, measured by infrared oculography after 6 months of treatment. Participants are assessed for persistent treatment effects 6, 18 and 30 months after end of treatment. Secondary outcome measures include other oculography parameters including double-step saccades, retinal imaging, visual acuities, physical disability, cognition and patient-reported outcomes.

Ethics and dissemination Clemastine is a registered and very well-established drug with well-known safety and side effects. The protocol was approved by the medical ethical committee of the Amsterdam UMC, location VUMC and the Dutch Central Committee on Research Involving Human Subject. Written informed consent is obtained from all participants. The results will be published in peer-reviewed medical scientific journals.

Trial registration number EudraCT: 2021-003677-66, ClinicalTrials.gov: NCT05338450.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study introduces a sensitive and specific method of measuring remyelination in multiple sclerosis by quantifying internuclear ophthalmoplegia with infrared oculography and includes a test to predict potential treatment response.
⇒ In contrast to previous optic neuritis studies this randomised controlled trial has a parallel design suited for interrogating sustained effects after discontinuation of treatment.
⇒ The long follow-up period of 3 years allows for studying and quantifying the long-term neuroprotective effects of clemastine through secondary outcome measures.
⇒ Complementary secondary outcome measurements include neurophysiological eye movement measurements, physical disability, cognitive measures, visual function, multimodal retinal imaging and patient-reported outcomes.
⇒ An important limitation is that subjects will not be permitted to drive during the study period due to Dutch law on use of clemastine. Future drug development on remyelination should take this hurdle to recruitment into consideration.

INTRODUCTION

In multiple sclerosis (MS) inflammation, demyelination and neurodegeneration lead to disability in persons affected.[1] Symptomatic recovery is hampered by failure of remyelination and neuroplasticity.[1] The first remyelination trial with a positive outcome in MS was focused on the optic nerve.[2] Testing axonal conduction velocity in the afferent visual pathway in people with multiple sclerosis associated optic neuritis (MS-ON) is currently the most established method of measuring remyelination in clinical trials.[3] The primary outcome for remyelination trials in MS-ON are pattern visual evoked potentials (pVEP) which are driven by the central macular response, vulnerable to a range of artefacts and highly dependent on timing of

the examination during the disease course.[3–5] Another limitation of measuring remyelination in MS-ON with pVEP is that it does not permit to extrapolate on remyelination outside the afferent visual pathway from the retina to visual area 1 and 2 in the visual cortex. Other reported outcome measures for remyelination trials include imaging approaches and composite scores clinical measures. Imaging studies on measuring remyelination disagree in which brain regions remyelination should be measured and a widely accepted imaging measure for remyelination which is sufficiently sensitive, specific and validated has yet to emerge.[6–8] Composite functional scores to measure remyelination mostly include established clinical measures, such as the Expanded Disability Status Scale, the Timed 25-Foot Walk, the Nine-Hole Peg Test and the Paced Auditory Serial Addition Test.[9] While these scores include tests that have proven their clinical relevance, they may not be sensitive enough to capture any and all improvement after remyelinating treatment. At the same time a composite score lacks the specificity of limiting the measurement of remyelination to affected systems that can show improvement. In order to strengthen remyelination trial design other sensitive and specific methods of measuring remyelination which offer complementary primary outcomes to pVEPs, reflect nerve function and permit for easier generalisation of remyelination in the central nervous system (CNS) are required.

Pioneering work by Elliot and Teresa Frohman on the internuclear ophthalmoplegia (INO) has laid the foundations for interrogating an anatomically and clinically well-defined symptom in MS.[10 11] Confirming this original research our group has demonstrated in different large cohorts that an INO can be found in about 25% of people with MS (pwMS).[12 13] A concise protocol for quantification of the INO has been validated for a multicentre setting.[14] This protocol selected highly reproducible quantitative measures with excellent intraclass correlations (ICCs >0.9). Moreover, the protocol expands from testing of the INO using a pro-saccadic task, to more complex tasks which permits indirect access to the CNS wide network governing eye movements.[15] In addition, this measurement method permits to address one of the big challenges for remyelination which is prediction of treatment failure.

Treatment failure in remyelination can be due to a number of factors, one of which is failure to compensate for the initial inflammatory injury, which leads to irreversible axonal degeneration.[1] In this situation attempted remyelination will be doomed to fail because there are no axons left to be remyelinated. A way out of this dilemma comes from an elegant observation made in the Frohman laboratory, the temperature dependence of Uthoff's phenomenon in INO.[16] The hypothesis is that if there is Uthoff's phenomenon, then there must be working axons.[17 18] Confirmation of this hypothesis comes from a trial using 4-aminopyridine (4AP) (fampridine).[19] Serum levels of fampridine peaked at 2–3 hours after oral administration which coincided with approximately a 20% improvement of a novel measure for eye movement speed in INO comparing drug with placebo.[19] Taken together these data suggest that (1) there are sufficient pwMS and INO (~25%) to be recruited for remyelination trials; (2) tests for selecting likely treatment responders are available (4AP or Uhthoff's phenomenon); (3) the validated DeMONS protocol provides a suitable primary outcome measure for remyelination of the medial longitudinal fasciculus (pro-saccadic task) and a number of secondary outcome measures for more widespread CNS remyelination.

The aim of this trial is to investigate the remyelinating effects of clemastine fumarate in patients with MS with INO, a clinical deficit which can be measured with high accuracy. Additionally, this study will investigate whether beneficial effects of clemastine persist after treatment and whether patients are protected from neurodegeneration in the long-term. Finally, the study will investigate whether treatment response to clemastine can be predicted with fampridine.

METHODS AND ANALYSIS

Study design

The RESTORE trial is a 36 months single-centre double-blind randomised placebo-controlled trial with 80 patients with MS and INO. Participants will be randomised 1:1 into two groups: group A and group B. Group A will receive 8 mg clemastine fumarate (4 mg two times a day) for 6 months (180 days). Group B will receive an equivalent amount of placebo for the same duration. Participants will be evaluated after 3 and 6 months of treatment. After 6 months of treatment participants will be taken off medication (study drug or placebo) and then reassessed at 12, 24 and 36 months. Figure 1 shows the timeline of the study. The RESTORE trial will be conducted at the MS Centre Amsterdam, Amsterdam UMC.

Eligibility criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria: a clinically definite

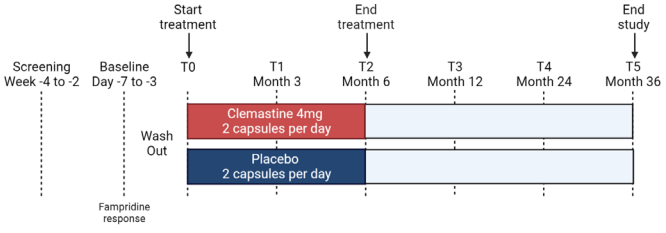

Figure 1 RESTORE timeline: After screening, participants are tested for fampridine response within 3 weeks at baseline. Participants are randomised prior to baseline visit and start treatment 3–7 days after baseline. Participants are on treatment for 6 months, after which treatment is discontinued. After the end of treatment participants take part in follow-up visits up to 36 months after the start of treatment.

diagnosis of MS; a diagnosis of internuclear ophthalmoparesis determined by the first infrared oculography at screening with either cut-off of 1.174 of the Versional Dysconjugacy Index area under the curve (VDI-AUC) of 15° saccades or 1.180 of the Versional Dysconjugacy Index peak velocity/saccadic amplitude (VDI-pV/Am) of 15° saccades[12]; age of 18–70 years (inclusive) and the ability to understand the purpose and risks of the study and provide signed and dated informed consent.

A potential subject who meets any of the following criteria will be excluded from participation in this study. MS-related exclusion criteria include: changes in immunomodulatory therapy for MS in the 6 months before inclusion into the study or clinical relapse of MS or high dosage corticosteroid use within 30 days before inclusion into the study.

Investigational medicinal product and medication-related exclusion criteria include: contraindications to clemastine use, such as known porphyria or hypersensitivity to clemastine; contraindications to fampridine use, such as hypersensitivity to fampridine or any of the excipients, history of epilepsy, kidney disease (glomerular filtration rate <50 mL/min), use of organic cation transporter 2 inhibitors or history of significant cardiac arrhythmias or conduction block; concomitant use of fampridine or any other formulation of 4AP or diamino4ap that cannot be temporarily suspended prior to each study visit; changes in the use of medication currently being investigated in remyelination trials within 6 months before screening, including but not limited to domperidone, liothyronine, quetiapine, testosterone and bazedoxifene or non-incidental use of CNS depressants including but not limited to hypnotics, anxiolytics, monoamine-oxidase inhibitors, tricyclic antidepressants, opioid analgesics and other antihistamines with sedating properties.

Medical history-related exclusion criteria include: a history of significant cardiac conduction block; history of malignancy of any organ system (other than localised squamous or basal cell carcinoma of the skin or adequately treated cervical cancer), treated or untreated, within the past 3 years, regardless of whether there is evidence of local recurrence or metastases; estimated glomerular filtration rate<50 mL/min/1.73 m^2; aspartate aminotransferase (AST), alanine aminotransferase (ALT) or alkaline phosphatase >2 times the upper limit of normal; any ophthalmological disease which may prevent accurate infrared oculography assessment; suicidal ideation or behaviour in 6 months prior to baseline; history of drug or alcohol abuse within a year prior to inclusion; clinically significant cardiac, metabolic, haematologic, hepatic, immunologic, urologic, endocrinologic, neurologic, pulmonary, psychiatric, dermatologic, allergic, renal or other major diseases that in the principal investigator's judgement may affect interpretation of study results or patient safety or a history of or presence of clinically significant medical illness or laboratory abnormality that, in the opinion of the investigator would preclude participation in the study.

Finally, other exclusion criteria include: pregnancy at the time of inclusion into the study or planning on breast feeding within the first 7 months after inclusion in the study; involvement in another study protocol simultaneously without prior approval; insufficient proficiency in reading Dutch or participant being unable or unwilling to suspend driving for a duration of 6 months.

Recruitment

Participants are recruited from three sources. First, patients in which INO was already established with infrared oculography will be recruited from other research projects at the MS-centre Amsterdam. Second, MS patients suspected of INO or with visual issues which may indicate INO (diplopia or issues of visually focusing) will be recruited through the Amsterdam UMC MS-centre outpatient clinic. Finally, patients with MS suspected of INO or with visual issues which may indicate INO will be recruited through the outpatient neurology departments of other centres in the Netherlands. Furthermore, information on the RESTORE trial is publicly available (European Union Clinical Trials Register and ClinicalTrials.gov), therefore interested patients may contact the investigators themselves. The first participant was included in the study on 30 August 2022. The last participant is expected to complete follow-up in 2026.

Study procedures

Infrared oculography

Infrared oculography is a modern eye tracking technology which allows accurate measurement and quantification of eye movements. This technique works by illuminating the eyes with infrared light and subsequently capturing the reflected light with an infrared camera. This allows for highly accurate tracking of eye movements. Because no visible light is used, this technique is non-invasive and well tolerated. Eye movement measurements will be performed using the EyeLink 1000 Plus Eye Tracker at the Department of Ophthalmology, Amsterdam UMC, by a trained scorer. Data will be acquired using dedicated software supplied by the manufacturer, including a calibration and validation procedure preceding the measurement.

A standardised protocol for quantification of saccadic eye movements has been developed by our research team which includes tasks for different types of eye movements.[14] The protocol consists of six tasks: fixation, horizontal pro-saccades, horizontal anti-saccades, horizontal express saccades, double-step saccades (horizontal and vertical) and repeated horizontal pro-saccades. Automated analysis methods are used to calculate parameters describing the characteristics of the saccadic eye movements. The analysis will be performed with custom-made software written in MATLAB (MathWorks, Natick, Massachusetts, USA). Parameters include saccadic latency (ms), pV (degree/ms), pV/Am and AUC of the saccadic trajectory. The pV, pV/Am and AUC parameters are used to calculate the VDI, which is the ratio of these parameters

Table 1 RESTORE assessment schedule

	Screening	Baseline	T0	T1	T2	T3	T4	T5
	−4 to −2 weeks	−3 to −7 days		3 months (±2 weeks)	6 months (±2 weeks)	12 months (±1 month)	24 months (±2 months)	36 months (±2 months)
Informed consent	X		Start treatment					
Eligibility criteria check	X							
Randomisation		X						
Medical history	X							
Physical and neuro-ophthalmological examination	X							
Saccadic eye movements	2x	2x		X	X	X	X	X
Fampridine treatment response		X						
Visual acuity	X			X	X	X	X	X
OCT		X		X	X	X	X	X
SDMT		X		X	X	X	X	X
EDSS	X			X	X	X	X	X
Questionnaires		X		X	X	X	X	X
Pregnancy test	X							
Blood samples	X			X	X	X		
Adverse event and compliance monitoring (interview)				X	X	X	X	X

EDSS, Expanded Disability Status Scale; OCT, optical coherence tomography; SDMT, Symbol Digit Modalities Test.

between the abducting and adducting eye. The VDI quantifies dysconjugacy of horizontal eye movements, which is the key feature of INO.

The VDI can be used to detect and quantify the severity of INO, which may be missed during clinical assessment. A previous study by our research team calculated the most sensitive measure and cut-off point of VDI for detecting INO in patients with MS, while retaining high diagnostic specificity.[12] A combination of VDI-pV/Am and VDI-AUC in 15° saccades resulted in the highest accuracy with 98% specificity. A threshold of 1.174 VDI-AUC or 1.180 VDI-pV/Am resulted in a prevalence of INO in MS of 24–34%.[12 13] Identical thresholds will be used to diagnose INO in the current study.

Infrared oculography will be performed twice at screening and baseline and once every follow-up visit. The measurement time is approximately 25 min.

Screening and baseline

Table 1 shows an overview of the assessments at each visit. At the screening visit an eligibility criteria check will take place including evaluation and documentation of medical history and medication use. The screening visit will include physical and neurological examination (including the Expanded Disability Status Scale (EDSS)), neuro-ophthalmological examination of eye movements and visual function (including high and low contrast vision) and laboratory tests to evaluate additional reasons for exclusion which may affect interpretation of study results or patient safety. The screening visit includes testing of saccadic eye movements with infrared oculography. This measurement provides our primary outcome measure, the VDI, which describes the ratio of the abducting eye to the adducting eye. The VDI will be determined twice at the screening visit in order to determine the individual physiological variation within the for this study relevant 2-hour time interval.

Within a time window of 3 weeks participants will be tested for baseline measures and fampridine treatment response. The saccadic eye movements will be tested before and 2 hours after receiving a single 10 mg dose of fampridine. During this 2-hour interval participants will undergo structural retinal imaging (optical coherence tomography, OCT) and questionnaires. Assessments that may be affected by fampridine, such as the Symbol Digit Modalities Test (SDMT), will be evaluated prior to the single fampridine dose. All participants in whom the VDI improves after fampridine will be flagged for later statistical analyses as likely treatment responders. Participants that already use fampridine prior to inclusion into the study may still participate, but are asked to suspend

fampridine for at least 24 hours prior to each study visit. The fampridine response test is followed by a 3–7 days wash out period, after which treatment will start.

Treatment period

Participants will be randomised to placebo or *clemastine fumarate*. T0 indicate the start of treatment with placebo or *clemastine fumarate* 4 mg orally two times a day for 6 months (180 days). Participants will be assessed for their saccadic eye movements and retinal OCT at T1 (3 months) and T2 (6 months). Additionally, visual acuity, SDMT, EDSS and various questionnaires (quality of life, visual issues and fatigue) will be assessed. Each visit will include an interview with study personnel monitoring for well-being, visual issues, possible side effects, new medication that may interfere with study medication and whether study medication is taken appropriately. Additionally, blood samples will be drawn to monitor for side effects and optionally additional blood samples may be stored in our MS Biobank on participant consent. After 6 months (180 days) treatment will be discontinued.

Follow-up

To investigate the long-term neuroprotective effects of clemastine patients will be reassessed at T3 (12 months), T4 (24 months) and T5 (36 months). These follow-up visits will include the same tests as in the treatment period. Each visit will include an interview monitoring for well-being, visual issues and new medication that may interfere with the study.

Outcome measures

Primary outcome

Our main study parameter is the relative change in INO between treatment and control groups as assessed by infrared oculography. This is measured by using the VDI-AUC parameter. The relative change in VDI from baseline will be compared between the treatment and control group at the end of treatment (6 months) and multiple follow-up periods (12, 24 and 36 months).

Secondary outcomes

In addition to the VDI-AUC, relative change in other VDI measures such as pV and pV/Am is also compared between the treatment and control group at 6 months, 12, 24 and 36 months.

Our main secondary outcome parameter is the predictive effect of fampridine on the change of INO in our treatment and control groups. This will be measured by comparing the aforementioned VDI changes in fampridine responders and non-responders.

Other secondary outcome measures include changes in other infrared oculography measures such as saccadic latency, proportion of errors in an anti-saccadic task, proportion of correct double-step saccades and error of the final eye position.

Furthermore, longitudinal measurements of retinal layer thickness by OCT will be used to determine whether clemastine can prevent MS-related retinal atrophy. Both the (peripheral) retinal nerve fibre layer and (macular) ganglion cell inner plexiform layer are included.

Additionally, the SMDT is included to determine whether clemastine treatment can improve cognitive processing speed. The EDSS is included to determine effects on physical disability. The effects on vision and visual functioning are quantified objectively by measurement of high and low contrast visual acuity and subjectively by the National Eye Institute Visual Functioning Questionnaire 25 and the neuro-ophthalmology questionnaire—Amsterdam UMC. Finally, effects on quality of life are estimated by the EuroQol 5D questionnaire and the prevalence of fatigue is estimated by the Checklist Individual (CIS20R) and Neurological Fatigue MS questionnaires.

Sample size calculation

Group size was calculated using a two-sided t-test for 80% power (β=0.2) at a significance level of 95% (α=0.05). An earlier study showed that fampridine could temporarily reduce VDI by 12.5–17.4%, depending on the type of VDI measure used (VDI offirst-pass amplitude (FPA) and peak velocity (pV), respectively).[19] The effect of clemastine on VDI measures is expected to be similar in order to be regarded as clinically relevant. Since the current study will use a different primary VDI measure (VDI-AUC) and may include more patients with less severe INO, a clinically relevant effect of clemastine is defined at 12% reduction in VDI for the current study. This is well above the within-subject variability on retesting, which was found to have a coefficient of variation of 1.1% for VDI-AUC of 15° saccades.[14] VDI-AUC measurement in patients with MS with INO in the Amsterdam MS cohort showed an average VDI-AUC of 1.32 with a SD of 0.21. A clinically relevant effect of −12% would therefore yield a reduction in VDI of 0.16.

Using this information group size calculates to 30 participants per group. The anticipated dropout is 20% over the entire trial period, requiring a minimum of 38 participants per group. The final group size was set to 40 participants per group, which resulted in a requirement of 80 study participants in total.

Statistical analysis

Primary outcome measures

Data will be analysed using an intention-to-treat approach including all patients randomised to the study for the principal analysis. Primary analysis will be performed after all participants completed 6 months of treatment. Secondary analysis will be performed at 36 months. Blinding will be maintained between the primary and secondary analysis.

The principal analysis will be performed using (mixed effects) linear regression models. The primary endpoint is treatment effect size of clemastine compared with placebo on VDI-AUC at the different follow-up visits, adjusted for the baseline VDI-AUC.

Secondary outcome measures

In order to estimate whether response to fampridine can predict clemastine treatment effect, fampridine response will be added to the (mixed effects) linear regression model. Fampridine response is defined as the difference between VDI parameters before and VDI parameters after fampridine administration. In addition, fampridine responders may be defined using a fampridine response cut-off value derived from receiver operating characteristic analysis using the fampridine response at baseline and variation in VDI parameters at screening. Subsequently fampridine response status may be entered into the (mixed effects) linear regression model in order to estimate whether fampridine response status may predict clemastine treatment response.

Other secondary parameters will be entered into (mixed effects) regression models as outcome variables in order to investigate the effect of clemastine treatment compared with placebo on the various secondary study parameters. Possible confounders such as age, sex, MS subtype, disease duration and fatigue will be added to regression models for the primary and secondary study parameters as deemed appropriate.

Patient and public involvement

Patients or the public were not involved in the design, conduct, reporting or dissemination plans of the trial.

ETHICS AND DISSEMINATION

The study will be conducted according to the principles of the Declaration of Helsinki (64th WMA General Assembly, October 2013) and in accordance with the Medical Research Involving Human Subjects Act and the Good Clinical Practice guidelines. The study was approved by the medical ethical committee of the Amsterdam UMC, location VUMC and written informed consent was obtained from all participants.

Clemastine is a very well-established drug, which means that safety and side effects are well-known. Clemastine is a safe drug with mild side effects, including fatigue and/or sleepiness. Possible sleepiness as a side effect legally prohibits study participants from driving a car for 6 months while using the study drug in the Netherlands. This applies to all participants whether on placebo or not because of blinding. This is anticipated to affect recruitment because of the impact on daily living activities. Due to the double-blind nature of this study this also applies to participants randomised to treatment with placebo. The assessments during study visits are non-invasive and have been tolerated well in other studies. Participants will be asked to participate in seven study visits in total over 3 years, which is unlikely to result in significant burden.

Publication will be in accordance with the basic principles of Dutch Central Committee on Research Involving Human Subjects statement on publication policy. The results will be presented at (inter)national scientific meetings. The results will be published in peer-reviewed medical scientific journals. In none of the publication forms, participant identity will be disclosed.

Contributors SH: methodology, investigation, writing—original draft, project administration. LJvR: conceptualisation, methodology, funding acquisition, supervision, writing—review and editing. AP: conceptualisation, methodology, funding acquisition, supervision, writing—review and editing, project administration. BMJU: conceptualisation, methodology, funding acquisition, supervision, writing—review and editing. JANB: conceptualisation, methodology, funding acquisition, software.

Funding This work was supported by Stichting VUmc Fonds grant number 399.

Competing interests AP reports personal fees from Novartis, Heidelberg Engineering, Zeiss, grants from Novartis, outside the submitted work; and AP is part of the steering committee of the OCTiMS study which is sponsored by Novartis. AP is part of the steering committee of Angio-OCT which is sponsored by Zeiss. He does not receive honorary as part of these activities. The NIHR BRC at Moorfields Eye Hospital supported AP. BMJU has received consultancy fees from Biogen Idec, Genzyme, Merck Serono, Novartis, Roche, Teva and Immunic Therapeutics. JANB is supported by the Dutch MS Research Foundation, grant nr. 18-1027.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iD

Sam Hof http://orcid.org/0000-0002-0453-6449

REFERENCES

1 Kuhlmann T, Moccia M, Coetzee T, *et al*. Multiple sclerosis progression: time for a new mechanism-driven framework. *Lancet Neurol* 2023;22:78–88.
2 Green AJ, Gelfand JM, Cree BA, *et al*. Clemastine fumarate as a remyelinating therapy for multiple sclerosis (ReBUILD): a randomised, controlled, double-blind, crossover trial. *Lancet* 2017;390:2481–9.
3 Petzold A, Fraser CL, Abegg M, *et al*. Diagnosis and classification of optic neuritis. *Lancet Neurol* 2022;21:1120–34.
4 Kleerekooper I, Del Porto L, Dell'Arti L, *et al*. Pattern ERGs suggest a possible retinal contribution to the visual acuity loss in acute optic neuritis. *Doc Ophthalmol* 2022;145:185–95.
5 Cordano C, Sin JH, Timmons G, *et al*. Validating visual evoked potentials as a preclinical, quantitative biomarker for remyelination efficacy. *Brain* 2022;145:3943–52.
6 Caverzasi E, Papinutto N, Cordano C, *et al*. MWF of the corpus callosum is a robust measure of remyelination: results from the ReBUILD trial. *Proc Natl Acad Sci U S A* 2023;120:e2217635120.
7 Tonietto M, Poirion E, Lazzarotto A, *et al*. Periventricular remyelination failure in multiple sclerosis: a substrate for neurodegeneration. *Brain* 2023;146:182–94.
8 van der Weijden CWJ, Biondetti E, Gutmann IW, *et al*. Quantitative myelin imaging with MRI and PET: an overview of techniques and their validation status. *Brain* 2023;146:1243–66.
9 Cadavid D, Mellion M, Hupperts R, *et al*. Safety and efficacy of opicinumab in patients with relapsing multiple sclerosis (SYNERGY): a randomised, placebo-controlled, phase 2 trial. *Lancet Neurol* 2019;18:845–56.
10 Frohman EM, Frohman TC, O'Suilleabhain P, *et al*. Quantitative oculographic characterisation of internuclear ophthalmoparesis in multiple sclerosis: the versional dysconjugacy index Z score. *J Neurol Neurosurg Psychiatry* 2002;73:51–5.
11 Frohman TC, Frohman EM, O'Suilleabhain P, *et al*. Accuracy of clinical detection of INO in MS: corroboration with quantitative infrared oculography. *Neurology* 2003;61:848–50.
12 Nij Bijvank JA, van Rijn LJ, Balk LJ, *et al*. Diagnosing and quantifying a common deficit in multiple sclerosis. *Neurology* 2019;92:e2299–308.

13 Hof SN, Loonstra FC, de Ruiter LRJ, *et al*. The prevalence of internuclear ophthalmoparesis in a population-based cohort of individuals with multiple sclerosis. *Mult Scler Relat Disord* 2022;63:103824.
14 Nij Bijvank JA, Petzold A, Balk LJ, *et al*. A standardized protocol for quantification of saccadic eye movements: DEMoNS. *PLoS One* 2018;13:e0200695.
15 Nij Bijvank JA, Hof SN, Prouskas SE, *et al*. A novel eye-movement impairment in multiple sclerosis indicating widespread cortical damage. *Brain* 2023;146:2476–88.
16 Davis SL, Frohman TC, Crandall CG, *et al*. Modeling Uhthoff's phenomenon in MS patients with internuclear ophthalmoparesis. *Neurology* 2008;70:1098–106.
17 Frohman TC, Davis SL, Beh S, *et al*. Uhthoff's phenomena in MS--clinical features and pathophysiology. *Nat Rev Neurol* 2013;9:535–40.
18 Petzold A, Wattjes MP, Costello F, *et al*. The investigation of acute optic neuritis: a review and proposed protocol. *Nat Rev Neurol* 2014;10:447–58.
19 Kanhai KMS, Nij Bijvank JA, Wagenaar YL, *et al*. Treatment of internuclear ophthalmoparesis in multiple sclerosis with fampridine: a randomized double-blind, placebo-controlled cross-over trial. *CNS Neurosci Ther* 2019;25:697–703.