Table 1: *Completed Randomised Controlled Trials in Progressive Multiple Sclerosis since 2014*

Trial year published	Intervention	Proposed mechanism	N (active vs placebo, unless stated); ratio	Duration (years)	Pre-trial progression, months	Multiple sclerosis duration (progressive disease duration), mean years	Participants with PPMS vs SPMS, n (%)	Age: inclusion criteria, mean (years); Female (n, %)	EDSS range: entry, mean	Participants with baseline gadolinium-enhancing lesions[♦], n/N (%)	Primary outcome (confirmation time); primary result No significant treatment effect was seen on these measures unless * is used	Secondary outcomes Those reporting significant benefit in active vs comparator group denoted by [+]
Phase 3												
INFORMS 2016[1] (NCT00731692)	Fingolimod 0.5mg daily	Oral sphingosine 1-phosphate (S1P) receptor modulator; induced lymphopenia via sequesters lymphocytes in lymph nodes	823 (336 vs 487); 1:1·4	3	≥12	6	823 (100%) PPMS	25-65; 49 398 (48%)	3.5-6.0; 4.67	107 / 820 (13%)	Time to composite of EDSS, and/or T25FW and/or 9HPT CDP (3m); HR 0.95 (77.2% vs. 80.3%, p=0.544)	Clinical: Time to EDSS CDP (3m); Time to T25FW CDP (3m), Time to 9HPT CDP (3m) PROs: EQ-5D; MSWS-12; PRIMUS; UFIS Biomarker: *MRI:* PBVC (month 36) (SIENA); Number of new/enlarging T2 lesions (month 36)[+]; Number of Gd-enhancing lesions (month 36)[+]; % free of Gd-enhancing lesions[+]; Number of new T1 hypointense lesions (month 36)[+]; % free of new T1 hypointense lesions[+]
MS-SPI 2016[2] (EudraCT:2013-002113-35)	High dose biotin (MD1003) 100mg three times daily	Activator of carboxylases which may promote myelin repair and neuroprotection via enhanced energy production.	154 (103 vs 51); 2:1	1	24	16	99 (64%) SPMS; 55 (36%) PPMS	18-75; 51 88 (54%)	4.5-7.0; 6.1	-	Proportion of patients with disability improvement on EDSS at month 9, confirmed at month 12 13 (12.6%) of treated patients vs. none of placebo group (p = 0.005) [+]	Clinical: Mean change in EDSS from randomisation to month 12; Change in EDSS FSS; Change in T25FW, 9HPT; % with EDSS and T25FW improvement; % with EDSS improvement; % with EDSS progression[+]; % with stable EDSS; Mean CGI at month 12 PROs: Mean SGI at month 12; Mean change in MSWS-12, SF-36 (health change)[+], MFIS
ORATORIO 2017[3] (NCT01247324 and NCT01412333)	Ocrelizumab 600mg intravenously every 6 months	Humanized monoclonal antibody that selectively depletes CD20-expressing B cells	732 (488 vs 244); 2:1	≥2 (event-driven)[†]	≥12	7 (3)	732 (100%) PPMS	18-55; 45 361 (49%)	3.0-6.5; 4.7	193 / 727 (27%)	Time to EDSS CDP (3m) HR 0.76 (160 [32.9%] vs. 96 [39.3%], p=0.03)[+]	Clinical: Time to EDSS CDP (6m)[+]; Change in T25FW (baseline to week 120)[+] PROs: Change in SF-36 (baseline to week 120) Biomarker: *MRI:* Change in T2 lesion volume (baseline to week 120)[+]; PBVC (week 24 to week 120)[+]
PROMESS 2017[4] (NCT00241254)	Cyclophosphamide 750 mg/m2 intravenously versus methylprednisolone 1 g every 4 weeks in year 1 every 8 weeks in year 2	Cyclophophamide: A CNS penetrant nitrogen mustard alkylating agent, inducing lymphopenia	138; 72 cyclophosphamide, 66 methylprednisolone; 1:1	2	12	13	138 (100%) SPMS	18-65; 48 90 (65%)	4.0-6.5; 5 (median)	-	Time to EDSS CDP (16w) aHR 0.61 (95% CI 0.31 to 1.22), p=0.16	Clinical: Sustained EDSS progression at 2 years; MSFC; ARR; % relapse-free patients
ASCEND 2018[5] (NCT01416181)	Natalizumab 300 mg intravenously every 4 weeks	Recombinant humanised monoclonal antibody against α4 integrin; inhibits leucocyte transmigration across the blood–brain barrier	887 (439 vs 448); 1:1	2 years (part 1) + open label extension (part 2)	24	17	887 (100%) SPMS	18-58; 47 550 (62%)	3.0-6.5; 6.0 (median)	210 / 884 (24%)	Time to composite of EDSS and/or T25FW and/or 9HPT CDP (6m) OR 0.86 (195 [44%] vs. 214 [48%], p=0.287)	**Part 1** Clinical: % with improvement in T25FW; % with CDP on individual EDSS FSS PROs: MSWS-12; ABILHAND; MSIS-29 physical score Biomarker: *MRI:* Change in whole brain volume between week 24 and 96

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												Part 2 Clinical: Proportion with multicomponent CDP⁺; Change in T25FW, 9HPT ⁺, EDSS from baseline to week 156; Change in 6-Minute Walk Test; SDMT scores from baseline to week 156 PROs: MSIS-29 physical score; Work Productivity and Activity Impairment Questionnaire score for multiple sclerosis from week 96 to 156 Biomarker: *MRI:* Change in whole brain volume from week 24 to 156; Change in grey matter brain volume from baseline to week 156; Number of new/enlarging T2 lesions from baseline to week 156
EXPAND 2018[6] (NCT01665144)	Siponimod 2mg daily	Selective inhibitor of sphingosine-1-phosphate (S1P) receptors 1 and 5; induces lymphopenia via sequestering lymphocytes in lymph nodes	1651 (1105 vs 546); 2:1	<3 (event-driven)†	24	17	1651 (100%) SPMS	18-60; 48 992 (60%)	3.0-6.5; 5.4	351 / 1248 (28%)	Time to EDSS CDP (3m) HR 0.79 (288 [26%] vs. 173 [32%], p=0.013)⁺	Clinical: Time to T25FW CDP (3m); Time to EDSS CDP⁺ (6m); ARR⁺; Time to first relapse⁺; Proportion of relapse-free patients; time to SDMT 4-point sustained worsening⁺ PROs: Change in MSWS-12 Biomarker: *MRI:* Total volume of T2 lesions (month 12, 24)⁺; Number of new/enlarging T2 lesions⁺; Number of Gd-enhancing lesions⁺; PBVC (month 12, month 24)⁺; Number of new/enlarging T2 lesions⁺
SPI-2 2020[7] (NCT02936037)	High dose biotin (MD1003) 100mg three times daily	[Mechanism as above]	642 (326 vs 316); 1:1	1	24	13 (from diagnosis)	415 (65%) SPMS 227 (35%) PPMS	18-75; 53 345 (54%)	3.5-6.5; 5.4	33 / 642 (5.1%)	Proportion of patients with disability improvement on EDSS or T25FW at month 12, confirmed at month 15 OR 1.35 (39 [12%] vs. 29 [9%], p=0.31)	Clinical: Time to EDSS CDP (12w); % change in mean T25FW between month 0 and 15; Mean difference CGI score at month 15; Mean change in EDSS subscores; Mean change in SDMT score PROs: Mean difference in SGI score at month 15; Mean change in remote monitoring of ambulatory activity; Mean change in MSQoL-54 (patient) and CAREQoL-MS (caregiver) Biomarker: *MRI*: MRI volumetric measures; Magnetic resonance spectroscopy; Spinal cord area imaging; *Fluid*: Mean change in serum neurofilament light concentration
Vermersch 2022[8] (NCT01433497)	Masitinib 4·5 mg/kg per day or 4·5 mg/kg per day increased to 6·0 mg/kg per day; two parallel groups	Oral tyrosine kinase inhibitor; inhibition of microglia, macrophage, and mast cell activity.	611 (200 masitinib 4·5 vs 101; 203 masitinib 6·0 vs 107); 2:1	2	24	14	360 (59%) non-active SPMS 251 (41%) PPMS	18-75; 49 316 (56%)	2.0-6.0; 5.3	-	Overall EDSS change from baseline (W12-96) in the masitinib 4.5mg/kg/day vs. placebo cohort δEDSS 0.001 in 4.5mg/kg/d group vs.0.098 in placebo, ΔLSM of −0.097 (p=0.026)‡	Clinical: Overall EDSS change from baseline (W12-96) in the masitinib 6.0mg/kg/day vs. placebo cohort; time to EDSS CDP (12w); Change from baseline on MSFC raw scores and component measures (T25FW, **9HPT⁺**, PASAT-3) PROs: MSQOL-54-mental health; SQOL-physical health; EQ-VAS
Phase 2												

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Tcelna presented 2016 (unpublished) (NCT01684761)	Tcelna Two annual course of 5 sub-cutaneous doses each year (at 0, 4, 8, 12, 24 weeks)	Tcelna consists of an autologous pool of myelin reactive T-cells (MRTC) expanded ex vivo	183	2	-	-	183 (100%) SPMS	18-60	3.0-6.0	-	Whole brain atrophy No significant benefit was reported	-
Spain 2017[9] (NCT01188811)	Lipoic acid 1200mg daily	Antioxidant with multiple biological functions including free-radical scavenging, metallic ion chelation, regeneration of intra- cellular glutathione, and repair of oxidative damage to macromolecules	51 (27 vs 24); 1:1	2	-	30	51 (100%) SPMS	40-70; 59 31 (61%) female	EDSS unlimited; 5.8	-	Whole brain atrophy Difference in atrophy 0.44%/year (-0.21% vs. -0.65%, p=0.002); 68% relative reduction⁺	Clinical: Change in EDSS, T25FW, SDMT; PROs: Activities of balance confidence; MSWS-12; SF-36 Biomarker: *MRI:* Atrophys of segmented brain (deep grey matter volume, cortical thickness, T2 lesion volume); Cervical spinal cord area; *Visual:* RNFL; Retinal ganglion cell plus inner plexiform layer
ReBUILD 2017[10] (NCT02040298)	Clemastine fumarate 5.36mg twice daily	First generation antihistamine— capable of inducing oligodendrocyte differentiation and myelination due to off-target antimuscarinic effect	50; cross-over trial (25 clemastine and 25 placebo during epoch 1, switched during epoch 2); 1:1	0.5	-	5 (RRMS population)	50 (100%) RRMS § No recent optic neuritis	18-60 (40) 32 (64%)	0-6.0 (2·2)	-	Reduction of P100 latency on VEP during treatment Reduction of P100 latency delay 1.7ms/eye (p=0.0048)⁺	Clinical: LCVA; SDMT PROs: MAF scale Biomarkers: *MRI:* Whole brain MTR, white matter MTR, white matter FA, MWF; T1, new/enlarging T2 lesions; *Visual:* RNFL on OCT
(NCT02228213) presented 2017 (unpublished)	MIS416 500mcg IV once weekly	Microparticulate immune response modifier targeting myeloid cells	93 (1:1)	1	-	-	93 (100%) SPMS	18-70	3.0-6.5	-	Change in neuromuscular function (MSFC, SDMT, SLVCA, 6MWT)	Clinical: Change in EDSS PROs: SF36; MSIS-29; NFI-MS; BPI Biomarkers: *MRI:* Whole brain atrophy; MTR; *Fluid:* Change in serum/PBMC/CSF immune biomarkers
INSPIRE Terminated 2017 (sponsor decision) (NCT02430532)	Dimethyl fumarate 120mg orally twice daily for 1 week, then 240mg orally twice daily thereafter	Immunomodulatory and neuroprotective properties by promoting nuclear factor erythroid-derived 2 pathway and by inhibition of the nuclear factor- kappa B signaling	58; 1:1	2	-	-	58 (100%) SPMS	18-58, 50.2. 36 (62%)	3.0-6.5	10 / 58 (17%)	Time to composite of EDSS, and/or T25FW and/or 9HPT CDP (6m)	Clinical: Change in SDMT score (baseline to 2 years) PROs: MSWS-12 (baseline to 2 years); ABILHAND (baseline to 2 years) Biomarker: *MRI:* Whole brain atrophy (baseline to 2 years)
SPRINT-MS 2018[11] (NCT01982942)	Ibudilast 100mg daily	Inhibits phosphodiesterases, macrophage migration inhibitory factor, and toll-like receptor 4	255 (129 vs 126); 1:1	2	24	10	134 (53%) PPMS 121 (47%) SPMS	21-65; 56 136 (53%)	3.0-6.5; 6.0	-	Whole brain atrophy Difference of 0.0009/year (-0.0010 ibudilast vs. -0.0019 placebo, p=0.04); 48% relative reduction	Clinical: % with 20-week EDSS CDP Biomarker: *MRI:* Transverse/longitudinal diffusivity in corticospinal tracts; MTR in normal-appearing brain tissue⁺; Cortical thickness⁺; *Visual:* RNFL

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Tourbah et al 2018[12] (NCT02220244)	High dose biotin (MD1003) 100mg three times daily	[Mechanism as above]	93 (65 vs 28); 2:1	0.5	-	12	Worsening optic neuropathy 34 (22%) SPMS 59 (63%) RRMS [b]	18-75; 41 50 (54%)	-	-	Mean absolute change from baseline to month 6 of best-corrected logMAR VA at 100% contrast in worse eye Mean difference -0.01983 (+3.1 vs. +1.8 letters), p=0.66	Clinical: % with improvement of VA; LCVA PROs: SGI; CGI; MSQOL-54; National Eye Institute 25-Item Visual Function Questionnaire (NEIVFQ-25) Biomarker: *Visual:* RNFL, macula volume; VEP; Automated perimetry
FLUOX-PMS 2019[13] (EudraCT: 2011-003775-11)	Fluoxetine 20mg daily	Selective serotonin-reuptake inhibitor; increased release of brain-derived neurotrophic factor from astrocytes and stimulation of astrocytic glycogenolysis	137 (69 vs 68); 1:1	2	-	13	77 (58%) PPMS 55 (42%) SPMS	25-65; 53 61 (45%)	3.0-6.5; 5.2	-	Time to T25FW or 9HPT CDP (3m) HR 1.25 [95% CI 0.79 to 2.49]	Clinical: % without T25FW CDP (3m); % without 9HPT CDP (3m); % with stable Hauser ambulation index; Change in SDMT, CVLT-II, COWAT PROs: BDI-II; MFIS Biomarker: *MRI:* Brain atrophy, grey matter volume, cortical grey matter volume, white matter volume; T2 lesion load; FA, mean diffusivity; *Visual:* RNFL, macular volume on OCT
SYNERGY 2019[14] (NCT01864148)	Opicinumab 3mg/kg, 10mg/kg, 30mg/kg, 100mg/kg IV every 4 weeks	Monoclonal antibody against LINGO1, hence potentially promoting remyelination	418 (45 3 mg/kg vs 95 10 mg/kg vs 93 30 mg/kg vs 92 100 mg/kg vs 93 placebo); 1:2:2:2:2	1.5	-	8	330 (79%) RRMS 88 (21%) active SPMS [¶]	18-58; 40 277 (66%)	2.0-6.0	180 / 415 (43%)	Percentage with confirmed disability improvement (3m): ≥1.0 point decrease in EDSS and/or ≥15% improvement in T25FW and/or dominant/non-dominant 9HPT, and/or PASAT-3 No difference in disability improvement with 3mg/kg (OR 0.98, p=0.96) or 100mg/kg (OR 0.98, p=0.96); some evidence of improvement with 10mg/kg (OR 1.79, p=0.064) and 30mg/kg doses (OR 2.06, p=0.022)[+]	Clinical: % with CDP (3m) on ≥1 of: EDSS, T25FW, dominant/non-dominant 9HPT, PASAT-3 Biomarker: *MRI:* Number of new/enlarging T2 lesions; Number of Gd-enhancing lesions; MTR, DTI; Whole brain volume
IPPoMS 2020[15] (NCT00950248)	Idebenone 2250mg daily	Synthetic quinone similar to coenzyme Q10 (CoQ10); potentially promotes mitochondrial function	73 (38 vs 35); 1:1	2	-	13	73 (100%) PPMS	18-65; 56 34 (47%)	1.0-7.0; 3.2	-	Change in Combinatorial Weight-Adjusted Disability Score (CombiWISE)|| Treatment difference 0.15 (p=0.74)	Clinical: Progression in EDSS-plus, T25FW, 9HPT, Scripps Neurological Rating Scale (SNRS), EDSS; *Progression in SDMT, MSFC* Biomarker: *MRI:* Enlargement of brain ventricular volume; *Visual:* RNFL thinning; *Fluid:* Changes in CSF albumin quotient, sCD14, lactate, GDF15, NFL
MS-SMART 2020[16] (NCT01910259)	Amiloride 5mg, fluoxetine 20mg, riluzole 50mg daily	Amiloride: acid-sensing ion channel blockade; reduces neuronal Na and Ca influx	445; 111 amiloride, 111 fluoxetine, 111	2	24	21	445 (100%) SPMS	25-65; 56 298 (67%)	4.0-6.5; 6.0	-	Whole brain atrophy Adjusted mean difference in atrophy vs. placebo 0%	Clinical: Changes in EDSS, T25FW, 9HPT, PASAT, MSFC, SDMT, high contrast visual acuity, Sloan LCVA from baseline to weeks 48 and 96; Time to first relapse

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		Fluoxetine – as above Riluzole: reduces glutamate release and antagonises voltage-dependent sodium channels	riluzole, 112 placebo; 1:1:1:1								(amiloride, p=0.99), -0.1% (fluoxetine, p=0.86), -0.1% (riluzole, p=0.77)	PROs: MSIS-29; MSWS;NFI; EQ-5D-5L; Neuropathic pain scores Biomarker: *MRI:* Number of new/enlarging T2 lesions at 96 weeks+; whole brain atrophy at 24 weeks
ARPEGGIO 2020[17] (NCT02284568)	Laquinimod 0.6mg or 1.5mg	Small molecule immunomodulator; reduced microglial and astrocytic reactivity and increases brain-derived neurotrophic factor	374 (139 0·6 mg vs 95 1·5 mg vs 140 placebo); 1·5:1:1·5	1	24	8	374 (100%) PPMS	25-55; 46 169 (45%) female	3.0-6.5; 4.5	58/374 (16%)	Whole brain atrophy Adjusted mean difference 0.016% (-0.454% laquinimod vs. 0.438% placebo, p=0.903)	Clinical: Time to EDSS CDP (3m); Time to T25FW CDP (3m); Change in T25FW from baseline to week 48; Change in BICAMS score from baseline to week 48; Time to CDP (3m and 6m) in at least 1 of 4 of: EDSS, T25FW, 9HPT, SDMT Biomarker: *MRI:* Number of new/enlarging T2 lesions at week 48+; New T1-hypointense lesions, change in T1-hypointense lesion volume+, changes in T2 lesion volume, thalamic, cortical, white matter and cervical cord atrophy, number of cervical cord T2 lesions, normal-appearing brain tissue average MTR
Petrou et al 2020[18] (NCT02166021)	Mesenchymal stem cells (MSC) intrathecal, intravenous	[Mechanism as above]	48 (16 intrathecal vs 16 intravenous vs 16 placebo); 1:1:1, crossover for second cycle after 6 months	1	-	13	7 (15%) PPMS 41 (85%) SPMS**	<65; 48 20 (42%)	3.0-6.5; 5.9	-	Differences in EDSS score change; proportion with treatment failure (increase in EDSS or deterioration in any functional system score) at 6 and 12 months % with treatment failure: 2 (6.7%) in MSC-IT; 3 (9.7%) in MSC-IV; 13 (41.9%) in placebo (p=0.0003 and p=0.0008 respectively) % with FSS deterioration: 9 (31%) in MSC-IT; 8 (27.6%) in MSC-IV; 23 (76.7%) in placebo (p=0.0002 and p=0.0004 respectively)	Clinical: Change in EDSS at 3, 6 months+; Treatment failure at 3 months+; Change in ambulation score at 3, 6 months+; Change in sum of functional scores at 3, 6 months+; ARR; Number of relapses (MSC-IT)+; Proportion relapse-free (MSC-IT)+; Change in T25FW+; 9HPT (non-dominant, MSC-IT)+; SDMT; PASAT (MSC-IT, 3 months+); OWAT (MSC-IT, 3 months+); NEDA 6 months+; NEDA-4+ Biomarker: *MRI:* Gd-enhancing lesions; T2 lesion load annualised rate of change (MSC-IT)+; PBVC; fMRI network connectivity strength (MSC-IV 3m, MSC-IT 6m)+; *Visual:* RNFL (MSC-IT left eye)+; % VEP latency change (MSC-IV right eye)+
FUMAPMS 2021[19] (NCT02959658)	Dimethyl fumarate 240mg daily	[Mechanism as above]	54 (27 vs 27); 1:1	1	12	14	54 (100%) PPMS	18-65; 55 21 (39%)	≤6.5	5 / 51 (10%)	Change in CSF NfL 0-48 weeks Treatment effect +99ng/L (95% CI −291.8 to 490.4 ng/L, p = 0.61; +35 DMF vs. -73 placebo, p=0.61)	Clinical: Change in EDSS, T25FW, 9HPT, SDMT Biomarker: *MRI:* Change in FA of normal-appearing white matter, MTR of lesions, mean thalamic volume, difference in number of new/ enlarging T2 lesions, PBVC; *Fluid:* Change in **CSF myelin basic protein (MBP)+**, soluble B-cell maturation antigen (BCMA), chitinase 3-like 1 (CHI3L1), soluble CD27 (sCD27), soluble CD14 (sCD14), IgG index, albumin quotient
RADIUS-P Completed 2021 (unpublished) (NCT03737812)	Elezanumab 400mg, 1800mg IV every 4 weeks	Monoclonal antibody to repulsive guidance molecule A (RGMa), an inhibitor of axon regeneration, neurite outgrowth, and remyelination	123 (40 1800 mg vs 40 400 mg vs 43 placebo); 1:1:1	48 weeks		-	64 (52%) SPMS	- 59 (48%)	6.0		Mean Overall Response Score (ORS) (EDSS, T25FW, dominant/non-dominant 9HPT) from baseline to week 52	Clinical: Disability Improvement Response Rate (EDSS+); Overall Response Score from baseline to week 36; LCVA; SDMT PROs: MFIS-5 Biomarker: *MRI:* whole brain atrophy; Cervical spinal cord volume change

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							59 (48%) PPMS				Least squares mean difference (95% CI) from placebo 400mg -0.01 (-0.48, 0.46), 1800mg 0.10 (-0.36, 0.56)	
Koch et al 2021[20] (NCT02308137)	Domperidone 10mg four times daily	D2 receptor antagonist, increasing serum prolactin, which may promote remyelination	110 (single-arm, Simon two-stage design)	1	12	22 (6)	62 (100%) SPMS	18-60; 53 47 (76%)	4.0-6.5; 6.1	-	Proportion with >20% worsening on T25FW at 12m compared to baseline. 22 (35%) had worsening of T25FW (higher than the futility threshold)	Clinical: Change in EDSS, 9HPT, SDMT PROs: MFIS; MSQOL-54
Koch et al 2021[21] (NCT02913157)	Hydroxychloroquine 200mg twice daily	Reduces the activation of human microglia and protects against experimental neurotoxicity.	49 (single-arm, Simon two-stage design)	1.5	-	10	35 (100%) PPMS	18-65; 56 13 (37%)	4.0-6.5; 5.6	-	Proportion with >20% worsening on T25FW at 12m compared to baseline. 8 (23%) had worsening of T25FW (lower than futility threshold)*	Clinical: EDSS; 9HPT; SDMT PROs: MFIS; MSQOL-54
Rust et al 2021[22] (NCT00799890)	Epigallocatechin gallate (EGCG) 1200mg daily	A polyphenolic green tea catechin with anti-inflammatory and neuroprotective properties	61 (30 vs 31); 1:1	3 + 1 OLE	5.8	10 (6)	23 (38%) PPMS 38 (62%) SPMS	18-65; 49 27 (44%)	3.0-8.0; 5.4	-	Whole brain atrophy 0.0092 vs. 0.0078 (p=0.670)	Clinical: EDSS CDP (6m); MSFC; 9HPT; T25FW; PASAT; ARR PROs: MFIS; Fatigue severity scale (FSS); BDI Biomarker: *MRI:* whole brain atrophy at month 36; Number of new/enlarging T2 lesions; Number/volume of Gd-enhancing lesions; *Visual:* OCT
MESEMS 2021[23] (NCT01606215)	Autologous bone marrow-derived mesenchymal stem cells: single intravenous infusion	[Mechanism as above]	144 (69 early treatment vs 75 early placebo and delayed treatment); 1:1	1	-	7	94 (65%) aRRMS; 33 (23%) aSPMS; 17 (12%) aPPMS ††	18-50; 39 87 (60%)	2.5-6.5; 4.0	61 (42%)	Total number of Gd-enhancing lesions over 24 weeks between treatment groups 1.16 for early MSC group vs. 1.24 for early placebo group (RR 0.94, p=0.78)	Clinical: ARR; Time to EDSS CDP; Proportion relapse-free, no evidence of sustained disability progression; Change in MSFC score; Change in SDMT score Biomarkers: *MRI:* Number of Gd-enhancing lesions over week 28, 36 and 48 compared with week 4, 12 and 24 within each group; CUALs (Gd-enhancing lesions or new/ enlarging T2 lesions); Volume of Gd-enhancing lesions; T2 lesion volume; Volume of black holes
(NCT03355365) Presented 2023 (unpublished)	Autologous bone marrow-derived mesenchymal stem cells: 6 intravenous infusions at 2 monthly intervals	[Mechanism as above]	51 (24 vs 27); 1:1, crossover after 1 year	2	-	-	-	-	3.0-6.5	-	Improvement in EDSS-plus (EDSS, T25FW or 9HPT) at 1 year No significant differences reported in the primary outcome.	Clinical: 6-minute walk test*; muscle strength test Biomarker: whole brain atrophy

Trial year published	Intervention	Proposed mechanism	N (active vs placebo, unless stated); ratio	Duration (years)	Pre-trial progression, months	Multiple sclerosis duration (progressive disease duration), mean years	Participants with PPMS vs SPMS, n (%)	Age: inclusion criteria, mean (years); Female (n, %)	EDSS range: entry, mean	Participants with baseline gadolinium-enhancing lesions$^{\varphi}$, n/N (%)	Primary outcome (confirmation time); primary result No significant treatment effect was seen on these measures unless * is used	Secondary outcomes Those reporting significant benefit in active vs comparator group denoted by $^{+}$
CogEx[24] 2023 (NCT03679468)	Cognitive rehabilitation (CR) + aerobic exercise (EX) vs. CR (and EX-sham) vs. EX (and CR-sham) vs. EX-sham + CR-sham	It is postulated that aerobic exercise may enhance the neuroplasticity of cognitive rehabilitation.	311 (77 vs 79 vs 80 vs 75 in respective groups); 1:1:1:1	0.25	Not required	15	84 (27%) PPMS 227 (73%) SPMS	25-65; 53 194 (62%)	<7.0; 6.0	-	SDMT correct responses at 12 weeks. There were no significant differences between groups; compared to the sham-CR and sham-EX group, the mean difference in SDMT was: −1·30 (95% CI −3·75 to 1·16) for CR + EX; −2·78 (−5·23 to −0·33) for sham-CR plus EX; and −0·71 (−3·11 to 1·70) for CR + sham-EX	Clinical: *Cognitive*: SDMT at 6 months; CVLT-II, BVMT-R; *Physical*: incremental exercise test*; 6MWT, actigraphy; dual task cost. PRO: HADS, MFIS, MSWS-12; EQ5D, MSIS-29*, Functional Assessment of Multiple Sclerosis.
EMBOLD press release 2023 (unpublished) (NCT03283826)	ATA188 Epstein-Barr Virus-directed allogenic cytotoxic T lymphocytes	Targets and depletes EBV-infected B-cells	103; 1:1	1	-	-	PPMS/ SPMS (non-active)	18-65; -	3.0-6.5; -	-	% with EDSS confirmed improvement at 12 months Failed to meet primary endpoint; 6% CDI for ATA188, 16% CDI for placebo.	

Characteristics of trials in progressive multiple sclerosis reported between April 6, 2014, and Jan 1, 2024. Trials are listed in order of publication or reporting (conference presentations or press-releases). For a fully referenced version of this table, including secondary outcomes, see appendix 1 (pp 1–11). 9HPT=nine-hole peg test. CDI=confirmed disability improvement. CDP=confirmed disability progression. CombiWISE=Combinatorial Weight-Adjusted Disability Score. EDSS=Expanded Disability Status Scale. FSS=functional system score. HR=hazard ratio. MSC=mesenchymal stem cells. NA=data not available. OR=odds ratio. PASAT-3=Paced Auditory Serial Addition Test 3. PPMS=primary progressive multiple sclerosis. RRMS=relapsing remitting multiple sclerosis. SDMT=symbol digit modalities test. SPMS=secondary progressive multiple sclerosis. T25FW=timed 25-foot walk. $^{\varphi}$participants with gadolinium-enhancing lesions at baseline, as a percentage of only those patients who underwent gadolinium-enhanced imaging. *Outcome reported to demonstrate a significant benefit as per the predefined criteria for significance in the trial. †Event-driven trial durations: in ORATORIO, participants received a minimum of five doses until 253 events of CDP had occurred; in EXPAND, the trial was terminated after 374 CDP events and more than 95% of participants had received treatment for longer than 12 months. ‡δEDSS denotes the least-squares mean difference in EDSS (positive value indicates disability progression); ΔLSM denotes the between-group difference in δEDSS (treatment effect; negative value favours masitinib). §Trial in patients with RRMS included as it is investigating a potential remyelinating treatment in patients with chronic optic neuritis – see main text for details. ¶In SYNERGY, active SPMS was defined as at least one of the following two events: clinical relapse, and gadolinium-positive lesions on MRI of the brain or spinal cord. ||CombiWISE integrates four clinical scales: EDSS, Scripps Neurological Rating Scale, T25FW, and 9HPT. **In Petrou et al 2020 (NCT02166021), active or worsening progressive multiple sclerosis was defined as at least two relapses or deterioration in EDSS and new MRI activity. ††In MESEMS, active multiple sclerosis was defined as: for RRMS, relapse or relapses with or without MRI activity within the past 12 months; for SPMS, progression of disease in the previous year, in presence of relapses or MRI activity; for PPMS, disease progression together with evidence of MRI activity within the past 12 months.

Table 2: *Ongoing Randomised Controlled Trials in Progressive Multiple Sclerosis*

Trial	Intervention	Proposed mechanism	N; Active: placebo ratio (unless stated)	Estimated completion	Trial duration (years)	PPMS/ SPMS	Entry EDSS	Age	Primary outcome, confirmation (months)	Secondary outcome
Phase 3										
MS-STAT2 (NCT03387670)	Simvastatin 80mg once daily	HMG CoA inhibitor; Cholesterol-independent (direct modulation of vascular endothelial and neuroglial function), and cholesterol-dependent pathways (modifying comorbidity) may be important	964; 1:1	2024	3-4.5	SPMS	4.0-6.5	25-65	Time to EDSS CDP (6m)	Clinical: Change in T25FW time; Change in 9HPT time; Change in BICAMS; Change in Sloan LCVA; Change in MSFC; mRS; Number/severity of MS relapses; Time to composite of EDSS and/or T25FW and/or 9HPT CDP (6m) PROs: MSWS-12v2; MsIS-29v2; Client Services Receipt Inventory Form; EQ-5D 5L scores; Chalder Fatigue Scale
PERSEUS (NCT04458051)	Tolebrutinib 60mg once daily	BTK inhibitor, suppressing B-cell and microglial activity	990; 1:1	2024	2-4	PPMS	2.0-6.5	18-55	Time to EDSS CDP (6m)	Clinical: EDSS CDP (3m); 3m change in 9HPT time; 3m change in T25FW time; Time to confirmed disability improvement (6m); Change in SDMT, CVLT-II PROs: MSQoL-54 Biomarker: *MRI:* New/enlarging T2 lesions; whole brain atrophy from month 6 to 48; *Fluid:* Change in plasma NfL, serum Chi3L1
HERCULES (NCT044116410	Tolebrutinib 60mg once daily	[Mechanism as above]	1,290; 1:1	2024	2-4	Non-relapsing SPMS	3.0-6.5	18-60	Time to EDSS CDP (6m)	
MAXIMS (NCT05441488)	Masitinib 4.5 mg/kg/day given orally twice daily	Oral tyrosine kinase inhibitor; inhibition of microglia, macrophage, and mast cell activity.	800; 1:1	2025	2	Non-relapsing SPMS/PPMS	3.0-6.0	18-60	Time to EDSS CDP (3m)	Clinical: Time to EDSS 7.0; Overall change in EDSS PROs: MSQOL-54; MFIS; HAM-D Biomarker: *MRI:* Change in baseline brain volume; New/enlarging T2 lesions; *Fluid:* Change in serum NfL and GFAP
FENtrepid (NCT04544449)	Fenebrutinib 200mg twice daily versus ocrelizumab 600mg IV every 6 months	Fenebrutinib – BTK inhibitor; ocrelizumab – humanised anti-CD20 monoclonal antibody	946; 1:1	2028	2	PPMS	3.0-6.5	18-65	Time to composite of EDSS and/or T25FW and/or 9HPT CDP (3m)	Clinical: Time to composite of EDSS and/or T25FW and/or 9HPT CDP (6m); Time to EDSS CDP (3m); Time to EDSS CDP (6m); Time to SDMT CDP (3m) PROs: MSIS-29 physical scale Biomarker: *MRI:* Change in total brain volume from week 24 to 120
O'HAND (NCT04035005)	Ocrelizumab 600mg IV every 6 months	[Mechanism as above]	1000; 1:1	2028	2	PPMS	3.0-8.0	18-65	Time to 9HPT CDP (3m)	Clinical: Time to 9HPT CDP (6m); Time to EDSS CDP (3m); Time to EDSS CDP (6m) Biomarker: *MRI:* T2 lesion volume change from baseline to week 120; whole brain atrophy from week 24 to 120
DanNORMS (NCT04688788)	Rituximab 1000mg IV every 6 months versus ocrelizumab 600mg IV every 6 months	Rituximab – chimeric (mouse/human) anti-CD20 monoclonal antibody; ocrelizumab – as above.	594; 2:1	2028	2	RRMS, active SPMS, active PPMS*	≤6.5	18-65	% without new or enlarging T2 white matter lesions	Clinical: % with EDSS CDP (6m); ARR; % with T25FW CDP (6m); % with 9HPT CDP (6m); % with SDMT CDP (6m); PROs: MSIS-29 physical scale; FSMC; EQ-5D Biomarker: *MRI:* % without Gd-enhancing lesions from month 6 to 24; Change in T2 and T1 white matter lesion volume; whole brain atrophy; *Fluid:* Change in serum NfL

Trial	Intervention	Proposed mechanism	N; Active: placebo ratio (unless stated)	Estimated completion	Trial duration (years)	PPMS/ SPMS	Entry EDSS	Age	Primary outcome, confirmation (months)	Secondary outcome
OCTOPUS Phase 2 / 3 (multi-arm multi-stage trial) (ISRCTN14048364)	Metformin 500mg twice daily, increased to 1000mg twice daily as tolerated. Alpha Lipoic acid (R/S-enantomer – R/S-ALA) 600mg once daily, increased to 600mg twice daily as tolerated.	Metformin activates AMP-activated protein kinase (AMPK) via multiple intracellular pathways. It promotes oligodendrocyte progenitor differentiation via AMPK-dependent mechanisms. R-ALA is a mitochondrial antioxidant. It may have additional anti-inflammatory effects mediated via inhibition of nuclear factor-κB (NF-κB), with reduced lymphocyte activity and toll-like receptor gene expression.	Stage 1; 375; 1:1:1 Stage 2: 1200; 1:1 (assuming single active arm continues to stage 2).	2028	Stage 1: 2 years Stage 2: continued for up to 5 years	PPMS / SPMS	4.0-8.0	25-70	Stage 1: whole brain atrophy Stage 2: time to EDSS-plus CDP (6m; EDSS, T25FW or 9HPT)	Stage 1: Clinical: time to CDP (6m) on each of EDSS, T25FW or 9HPT; change in SDMT; MSFC Z-score; SLCVA; relapse rate PRO: MSIS-29v2; MSWSv2; MFIS-21; CFQ; neuropathic pain scale; neuropathic rating scale; EQ 5D 5L Health Questionnaire; CSRI Biomarker: brain regional atrophy; cervical cord atrophy; T2LV
SAR441344 (NCT06141486)	IV Frexalimab	Anti-CD40L monoclonal antibody; blocks the CD40-CD40L costimulatory pathway necessary for T-cell, B-cell, macrophage and dendritic cell activation.	858	2028	2.3 to 4.3 years (event driven)	Non-relapsing SPMS	6.0-6.5	18-60	Time to EDSS-plus CDP (6m; EDSS, T25FW or 9HPT)	Clinical: time to EDSS-plus CDP (3m; EDSS, T25FW or 9HPT); time to CDP (3m or 6m) on each individual component (EDSS, T25FW, 9PHT); time to EDSS confirmed disability improvement; change in SDMT from baseline; relapse rate PRO: MSIS-29v2; Fatigue multiple sclerosis (MS)-8a) Biomarker: MRI: new/enlarging T2 lesions; whole brain atrophy; Fluid: plasma NfL; neutralising antibodies; frexalimab plasma concentrations
BEAT-MS (NCT04047628)	Autologous haematopoietic stem cell transplantation (6 day BEAM protocol) vs. best available therapy	BEAM protocol includes carmustine, etoposide, cytarabine and melphalan, plus rabbit anti-thymocyte globulin, to achieve myeloablation and immunoablation; followed by autologous graft infusion	156; 1:1	2029	6	RRMS, active SPMS†	≤6.0	18-55	Relapse-free survival up to 36 months	Clinical: ARR; EDSS CDP (6m); EDSS confirmed disability improvement (6m) Biomarker: *MRI:* whole brain atrophy; *Fluid:* Change in serum NfL
STOP-MS Phase 2 / 3 (multi-arm multi-stage trial) (ACTRN12623000849695)	Spironolactone 50mg twice daily; famciclovir 500mg twice daily, or placebo.	Spironolactone inhibits EBV protein SM, reducing viral capsid antigen synthesis, capsid formation and EBV virion production; famciclovir is a prodrug of peniciclovir, a nucleotide analogue with improved CNS-penetrance compared to acyclovir and established activity against herpes viruses.	Stage 1: 150; 1:1:1 Stage 2: 350; 1:1 (only 1 intervention vs. placebo continued)	-	Stage 1: 6 months Stage 2: 3 years	PPMS / SPMS	4.0-8.0	25-70	Stage 1: Co-primary: frequency of salivary EBV DNA and serum EBNA1 antibody titres. 10% reduction compared to placebo required for an intervention to progress to stage 2; intervention with largest reduction will be selected for Stage 2. Stage 2: time to EDSS-plus CDP (6m; EDSS, T25FW or 9HPT)	Clinical: MSFC Z-score; 9HPT; T25FW; time to CDP (6m) on EDSS alone; time to first relapse PRO: Neuropathic pain scale; MSWSv2; MSIS-29; MFIS-21; EuroQoL
Phase 2										

Trial	Intervention	Proposed mechanism	N; Active: placebo ratio (unless stated)	Estimated completion	Trial duration (years)	PPMS/ SPMS	Entry EDSS	Age	Primary outcome, confirmation (months)	Secondary outcome
ACTIMUS (NCT01815632)	Early or late (1 year) infusion of autologous MSC	Proposed immunomodulatory and neurotrophic effects	80 (crossover trial); 1:1	Unknown	2	PPMS OR SPMS	4.0-6.0	18-65	Global evoked potential derived from multimodal evoked potentials (visual, sensory, motor, and brainstem auditory) from infusion to end of study	Clinical: Time to EDSS progression; MSFC PROs: MSIS-29 Biomarker: *MRI:* Lesion load; Brain and spinal cord atrophy; Change in mean diffusivity; *Visual:* RNFL, macular volume on OCT
CHARIOT (NCT04695080)	Cladribine 3.5mg/kg in two treatment courses 12 months apart	Purine analogue; pulsed selective depletion of B- > T-lymphocytes.	200; 1:1	2024	2	Advanced PMS	6.5-8.5	18+	9HPT speed at 24 months; proportion who do not deteriorate on 9HPT at 24 months	Clinical: Change in EDSS; Change in ARAT upper limb function test score; Change in ABILHAND score; Change in T25FW time; Change in Sloan LCVA score; Change in SDMT score; Change in NFI-MS score PROs: MSIS-29v2 quality of life score; EQ-5D-5L; WPAI-GH score Biomarker: *MRI:* whole brain atrophy from month 6 to 24; New hypointense T1 lesions over 24 months; regional atrophy (Cortical, deep grey matter, thalamic, hippocampal, ventricular, spinal volumes); proportion slowly expanding lesions; *Fluid:* sNFL
CALLIPER (NCT05054140)	IMU-838 Vidofludimus calcium 45mg daily	Dihydroorotate dehydrogenase inhibition; limits lymphocyte proliferation via pyrimidine depletion	450; 1:1	2024	2 + 8 OLE	PPMS/SPMS	3.0-6.5	18-65	Whole brain atrophy	Clinical: EDSS CDP; Safety
LAPMS (NCT03161028)	Lipoic acid 1200mg daily	Antioxidant with multiple biological functions, including free-radical scavenging, metallic ion chelation, regeneration of intracellular glutathione, and repair of oxidative damage to macromolecules	115; 1:1	2024	2	PPMS/SPMS	3.0-6.5	18-70	T25FW change from baseline to year 2	Clinical: Change in 2-minute timed walk; Fall count Biomarker: *MRI:* whole brain atrophy from month 0 to 24
(NCT05013463)	Hydroxychloroquine 200mg twice daily and indapamide 2.5mg daily	Hydroxychloroquine: Reduces the activation of human microglia and protects against experimental neurotoxicity; indapamide: thiazide-like diuretic with proposed antioxidant and neuroprotective properties in *in vitro* studies	35; Single arm Simon 2-stage design	2024	1.5	SPMS	4.0-6.5	18-60	T25FW change from 6 months to 18 months	Clinical: Change in 9HPT time; Change in SDMT score; Change in EDSS PROs: MFIS; MSQoL-54
NACPMS (NCT05122559)	N-acetyl cysteine 1200mg three times daily	Precursor to the antioxidant glutathione	98; 1:1	2025	1.25	PPMS/SPMS	3.0-7.0	40-70	Whole brain, thalamic and cord atrophy	Clinical: Change in 9HPT, T25FW, SDMT Biomarker: *Wearables:* Imaging metrics and changes captured by a wearable multi-sensor device
(NCT05630547)	SAR443820	CNS-penetrant small molecule inhibitor of receptor-interacting protein kinase 1 [RIPK1]. RIPK1 activity regulates inflammatory responses in microglial and astrocytes	168; 1:1	2025	2	PPMS/SPMS/ RRMS	2.0-6.0	18-60	Change in sNfL from baseline to week 48 (part A), week 96 (part B)	Clinical: Time to CDP (3m) on EDSS, 9HPT, T25FW; Change in *EDSS-Plus* from baseline; ARR PROs: MSIS-29v2m; MSWS-12m Biomarker: *MRI:* New/enlarging T2 lesions; whole brain atrophy; Number, volume, intensity of slowly expanding lesions; Number of Gd-enhancing lesions, phase rim lesions

Trial	Intervention	Proposed mechanism	N; Active: placebo ratio (unless stated)	Estimated completion	Trial duration (years)	PPMS/ SPMS	Entry EDSS	Age	Primary outcome, confirmation (months)	Secondary outcome
MACSiMiSE-BRAIN (NCT05893225)	Metformin 850mg orally twice to three times a day (Mechanism as above)	[Mechanism as above]	120; 1:1	2026	2	Non-active PPMS / SPMS on stable DMT or no DMT	2.0-6.5	18-70	T25FW (change from baseline, continuous variable)	Clinical: change from baseline in: SDMT; 9HPT; EDSS; change in ORS based upon EDSS, T25FW, 9HPT; 2 minute walk test; PRO: EQ-5D-5L; MSIS-29; caregiver strain index; Health resource questionnaire. Biomarker: whole brain atrophy; T2LV; T1LV; diffusion tensor imaging; number of SWI-positive lesions.
CLASP-MS (NCT05961644)	Cladribine 1.8mg/kg administered subcutaneously over 6 visits every 5-6 weeks for 6 months	[Mechanism as above]	118; 1:1	2027	2	Non-active SPMS	3.5-7.5	30-65	Whole brain atrophy	Clinical: time to CDP on a composite of EDSS, T25FW, or 9HPT; SDMT, CVLT-2 PRO: MSQOL-54 Biomarker: *imaging* – Gd+ lesions; QSM+ rim lesions; cervical spine volume change; *Fluid* – sNFL, sGFAP, serum cytokine profile; CSF OCB status.
NORSEMAN (NCT05740722)	Nicotinamide Riboside – a nicotinamide adenine dinucleotide (NAD) precursor.	It is proposed that increasing neuronal NAD may improve mitochondrial function.	300; 1:1	2027	2.5	PPMS or SPMS	3.0-6.5	18-65	EDSS-plus sustained disability progression (EDSS, 9HPT or T25FW)	Clinical: EDSS sustained disability progression; 9HPT sustained disability progression; T25FW sustained disability progression Biomarker: T2LV; T2 lesion number; whole brain atrophy
HCQPET (EUCTR2022-003170-23-FI)	Hydroxychloroquine 200mg twice daily	Mechanism as above	30; 1:1	-	1	PPMS or non-active SPMS	3.5-7.0	35-65	Change in supratentorial white matter PET-TPSO signal from baseline end of study	Clinical: T25FW, 9HPT; neuropsychological assessment PRO: RAND-36, MSIS-29, MFIS, FSS Biomarker: *Imaging*: whole and regional brain atrophy; T1LV and T2LV; MR diffusion-tensor imaging; number of chronic active lesions detected by TPSO-PET or QSM iron rims; TPSO-PET signal at the rim of active lesions; UCB-J PET signal to measure synaptic density; *Fluid:* sNfL; sGFAP

Characteristics of trials in progressive multiple sclerosis that are ongoing as of Jan 1, 2024. Trials are listed in order of predicted publication or reporting. As all trials are ongoing, they are referenced only by their registration number. For a version of this table including secondary outcomes, see appendix 9HPT=nine-hole peg test. AMPK=adenosine monophosphate-activated protein kinase. BEAM= Carmustine, Etoposide, Cytarabine and Melphalan protocol conditioning prior to autograft]; BTK=Bruton tyrosine kinase. CDP=confirmed disability progression. EDSS=Expanded Disability Status Scale. PPMS=primary progressive multiple sclerosis. RRMS=relapsing-remitting multiple sclerosis. SPMS=secondary progressive multiple sclerosis. T25FW=timed 25-foot walk. *In DanNORMS, active SPMS is defined according to relapse or radiological activity in the previous 12 months, and active PPMS according to relapse, radiological activity, or elevated CSF or serum neurofilament light chain in the previous 12 months. †In BEAT-MS, active SPMS is defined according to at least two episodes of disease activity (clinical or radiological) in the previous 36 months, with one episode being a relapse despite oral disease-modifying therapy treatment, and one episode occurring in the previous 12 months.

Table 3: Key clinical outcome measures used in trials for PMS

Outcome measure	Description	Clinically meaningful change	% with Confirmed Disability Progression (6m) in 2 year trials	Comment	Examples
Clinician assessed outcomes					
Expanded Disability Status Scale (EDSS)	A clinician-rated ordinal scale ranging from 0 (no symptoms or signs) to 10 (death due to MS).	A 0.5 or 1.0-point increase, depending on the baseline disability score.	13-29%.[25,26]	In trials of PMS, EDSS primarily reflects lower limb function and recent publications have highlighted potential issues with reliable; it is, however, accepted by regulatory authorities.[27–30]	EXPAND and ORATORIO: positive primary outcomes have led to the licensing of siponimod and ocrelizumab.[3,6]
Performance-based outcomes:					
Timed 9-hole peg test (9HPT)	An upper limb measure assessing the time required to place 9 pegs in a board and remove them again; repeated twice with each hand. Maximum time per trial: 300 seconds	≥ 20% worsening from baseline.[31]	8-12%.[25,26]	Allows the inclusion of non-ambulant PMS in trials – a previously neglected group. There is a lack of consensus around analytical approaches (average of both hands vs. either hand vs. dominant hand to define 20% change); greater short-term fluctuations compared to the EDSS.[28,32]	Primary outcome for the ongoing O'HAND and CHARIOT-MS (with time to 20% CDP used in O'HAND, and a continuous speed at 24 months used for CHARIOT-MS). In ASCEND, natalizumab significantly delayed time to 20% CDP on 9HPT (secondary outcome).[5]
Timed 25-foot walk (T25FW)	A lower limb measure assessing the time required to walk 25-feet. It is repeated twice and averaged. Maximum time per trial: 300 seconds	≥ 20% worsening from baseline.[33]	25-32%.[25,26]	May show greater short-term fluctuations compared to EDSS.[28]	ORATORIO: lower mean change in 25FW for ocrelizumab compared to placebo; EXPAND and ASCEND: no significant benefits on 25FW CDP.[3,5,6]
Sloan low contrast visual acuity (SLCVA)	Low contrast letters, typically at 2.5% with either monocular or binocular vision, are read from standardised charts; total correct letters determines the score (maximum 70).	≥ 7-point worsening from baseline.[34]	-	The visual system is particularly suited to remyelination therapies, hence SLCVA may be an important outcome for such trials.	ReBUILD: post-hoc analysis suggested potential significant benefit with clemastine compared to placebo on SLCVA (2.5%, continuous variable).[10]

Symbol digit modality test (SDMT)	Participants decode rows of symbols into digits, using a key; total correct verbal responses in 90 seconds determines the score (maximum 110).	≥ 4-point worsening from baseline.[35]	31%*.[36]	Well-validated and available in multiple languages; currently preferred outcome to assess information processing speed.[35]	EXPAND: post-hoc analysis suggested siponimod reduced the risk of SDMT CDP (HR 0.79, 95% CI 0.65 to 0.96);[36] the CogEx trial used SDMT at 12 weeks (analysed as a continuous variable) as the primary outcome – no benefit was found for cognitive rehabilitation and/or aerobic exercise compared to placebo.[24]
Revised Brief Visuospatial Memory Test (BVMT-R)	Participants are shown 6 simple geometric shapes for 10 seconds, then must draw them immediately from memory (3 consecutive attempts, maximum score 36).	-	-	Reliable and valid across multiple languages; lack of consensus on clinically meaningful change limits time-to-event analysis.[37]	EXPAND: post-hoc analysis found no significant difference between siponimod and placebo (BVMT-R as a continuous variable).[36]
Californian Verbal Learning Test (version 2; CVLT-2):	Participants listen to a list of 16 words, and are assessed by immediate verbal recall (5 consecutive attempts, maximum score 80).	-	-	As for the BVMT-R – reliable and valid in multiple languages, but lacks consensus on clinically meaningful change.[37]	FLUOX-PMS: secondary analyses found no significant difference with fluoxetine compared to placebo on CVLT-2 (consistent with the primary outcome).[13]
Multi-component outcomes					
e.g. EDSS-plus	Typically define progression if clinically significant worsening is achieved on: EDSS and/or T25FW and/or 9HPT.[38]	A 0.5 or 1.0 point increase on EDSS, and/*or* ≥ 20% worsening on *either* 9HPT and/or T25FW	30-54%.[25,26]	Higher event rates increase trial power; however, multi-component outcomes incorporate measurement error of each individual component; currently lack acceptance with regulatory authorities.[25,26,39,40]	ASCEND: natalizumab did not show significant benefit compared to placebo on the primary multicomponent outcome of EDSS-plus, despite a positive secondary outcome on 9HPT alone; INFORMS: fingolimod did not show significant benefit compared to placebo on the same multicomponent outcome, or any of its subcomponents. [1,5]
Patient reported outcomes					
Multiple Sclerosis Impact Scale-29 (MSIS-29)	An MS-specific questionnaire – participants rate the impact of their MS during the last two weeks on ordinal scales. 20 items relate to physical health, and 9 to psychological health, with higher scores indicating more severe impairment. (Version 1 scores from 1 to 5, Version 2 from 1 to 4	A worsening of 8-points on the MSIS-29, or on its physical-subscale (v1).[41,42]	~30%†[43]	There is currently a lack consensus regarding a core set of PROs to be used in MS clinical trials; further data are required to establish clinically meaningful changes on each PRO, and to further assess the validity, reliability and responsiveness of each outcome to treatment interventions.[44]	ASCEND and MS-SMART: consistent with the primary analyses, no significant differences were seen on MSIS-29 physical subscores.[5,16] In EXPAND, siponimod reduced the risk of a 7.5 point increase by 21.8% (HR 0.78 [0.64 to 0.95]).[43]

	– hence maximum 145 for v1, 116 for v2).				
Multiple Sclerosis Walking Scale (MSWS-12)	An MS-specific questionnaire – participants rate the impact of their MS on lower limb function using ordinal scales. Higher scores indicate more severe impairment. (Version 1 scores from 1 to 5, Versions 2 reduces 3 items to 1 to 3 – hence maximum of 60 for v1, but 54 for v2).	A worsening of 8-points (v1).[45]	~30%†[43]		EXPAND: post-hoc analyses found a −1·77 (−3·59 to +0·05) difference with siponimod compared to placebo; siponimod reduced the risk of an 8-point increase by 24.5% (HR 0.75 [0.62 to 0.92])[43] INFORMS and ASCEND: neither fingolimod nor natalizumab showed significant benefit compared to placebo (consistent with the primary outcomes).[1,5,6]
Medical outcomes study 36-item short form health survey (SF-36):	A generic questionnaire assessing overall health status and quality of life. Two standardised summary scores (physical and mental health) are usually reported – scored 0-100, with lower scores indicating worse quality of life; a mean score of 50 (s.d. 10) corresponds to that of the general US population.	A worsening of 5 points (half a standard deviation) on the physical and mental health summary scores (though not validated in MS cohorts).[46,47]	-		***Examples*:** ORATORIO: contrary to the primary outcome, ocrelizumab did not show significant benefits compared to placebo on the SF-36 physical summary score; similarly, in MS-SPI, biotin treatment was not associated consistent benefits on SF-36 subscores compared to placebo, despite the positive primary outcome.[2,3]
Multiple Sclerosis Quality of Life-54 (MSQOL-54):	Based on the SF-36, but with 18 additional items added to make it more specific to MS-related disability; as for the SF-36, standardised physical and mental health summary scores are usually reported (scored 0-100, with lower scores indicating worse quality of life).	-	-		***Examples***: SPI-2: consistent with the primary outcome, an exploratory analysis found no significant differences between biotin and placebo on MSQoL54 physical or mental health summary scores; Vermersch et al: contrary to the positive primary outcome, no significant differences between masitinib and placebo on either MSQOL-54 summary score.[7,8]

Details of physician-assessed, performance-based and patient-reported outcome measures commonly used in recent randomised controlled trials in progressive multiple sclerosis. Reported definitions of clinically meaningful change, their expected event rate in PMS populations, and examples from published clinical trials are included. Data for the proportion of patients with 6-month CDP are taken from reported clinical trials – see fully referenced article in the appendix for details. Where such data have not been previously reported, this column is left blank. *Data for SDMT CDP represent the proportion of patients with worsening confirmed at 6 months, and sustained until the end of study. †Data from EXPAND, in which median time in study was 21 months; a cut-off of 7·5 points was used to define CDP on the MSIS-29, and 8 points on the MSWS-12.Where data is not available, this is represented by a -.

Table 4: Advanced imaging techniques being evaluated as outcome measures in progressive multiple sclerosis

Imaging modality	Signal source/measure	Pathology validation	Advantages	Disadvantages
Compartmentalised CNS inflammation – Imaging Chronic Active Lesions				
Paramagnetic rim lesions (PRLs)	Detection of iron accumulated in active microglia / macrophages at the rim of lesions via T2* or susceptibility weighted images, and quantitative susceptibility mapping.[48]	Human[49]	Sequences available on clinical scanners; short acquisition (<5 minutes); published guidelines on reporting available[50]	Longitudinal dynamics of PRL development and resolution remain unknown; limited data on response to treatment
Slowly expanding lesions (SELs)	Automated pipelines apply deformation-based techniques to detect consistent concentric expansion of white matter lesions across co-registered longitudinal imaging.[51,52]	None currently	Required sequences are already obtained in standard clinical and research protocols; automated pipelines available for analysis	Requires consistent acquisition parameters over at least 3 timepoints; lack histological validation; overlap between SELs and PRLs at the lesion level is low; they may represent similar, but different, biological processes.[53,54]
Positron Emission Tomography (PET)	Several radiotracers with specificity to microglia are available, including those targeting translocator protein 18 kDa (TSPO), and cyclo-oxygenase-2 (COX-2).	Animal[55] Human[56]	Radiotracer ligands for translocation protein 18kDa (^{3}H-PK11195 and ^{3}H-PBR28) have been histologically validated as biomarkers of myeloid cells within active and chronic active lesions.[56]	Specificity of TSPO signal to human activated microglia has been questioned; likely to represent microglial/macrophage density rather than activation state.[57,58] Limitations due to radiotracer production, cost, harmonization of analytical methods, low spatial resolution, and physiological properties of different tracers
Myelin imaging techniques				

Magnetization transfer ratio (MTR)	Ratio representing exchange of macro-molecular bound and free protons	Animal[59] Human[60]	Ease of acquisition; short acquisition time; extensive experience already in clinical trials	Not completely specific to myelin, requires within-patient and multi-centre calibration, susceptible to field inhomogeneity and other pathological processes, such as oedema, inflammation and axonal density.
Quantitative Magnetization Transfer Imaging (qMTR)	Quantitation of macromolecule bound and free protons exchange	Animal[61] Human[62]	More reproducible across scanners, and less sensitive to field inhomogeneity and T1 relaxation effects compared to MTR	Longer acquisition time, can have more limited field of view, less validated in multi-centre studies compared to MTR
Diffusion tensor imaging (DTI)	Water diffusion modelled in tensor with myelin sensitive measures perpendicular to axons (fractional anisotropy, mean diffusivity, radial diffusivity)	Animal[63] Human[64]	Easily acquired, with established measurement values. Some experience with multi-centre implementation.[11]	Technically difficult to apply in multi-centre fashion. Not pathologically sensitive. Some difficulty interpreting changes when crossing fibres are present
Myelin water imaging (MWI)	Distribution of T2 relaxation from water trapped in myelin bi-layers. Myelin water fraction is derived from the short T2 component (myelin water) over total water content	Animal[65] Human[66]	Can be more specific for myelin than other techniques. Sensitive to white matter demyelination and MS lesions.	Long acquisition time and complex analysis. Has not been extensively applied in multi-centre studies.
Direct Visualization of Short Transverse Relaxation Time Component (ViSTa)	Employs double inversion radiofrequency to capture short T2* and short transverse relaxation of myelin water.	None currently	Whole brain acquisition in clinically feasible scan times. Quantitative technique.	Has not been extensively applied in multi-centre studies. Limited pathological validation.
Quantitative susceptibility mapping (QSM)	Acquires diamagnetic signal from myelin related susceptibility	Animal[67] Human[68]	Fast acquisition time; images can be created by saving phase images during SWI or T2* acquisitions.	Significant post-processing required, which is not fully standardized; has not been extensively applied in multi-centre studies.

Positron Emission Tomography (PET)	Several radiotracers with specificity to myelin components or associated axonal components are available including 1,4-bis(p-aminostyryl)-2-methoxy benzene (BMB), [(^{11}C)] 2-(4'-methylaminophenyl)-6-hydroxybenzothiazole (PIB), [(^{11}C)] Case Imaging Compound (CIC),[(^{11}C)] N-methyl-4,4'-diaminostilbene (MeDAS)	Animal[69–71] Human[72,73]	Might provide a more specific measure of myelin content compared to other techniques, depending on radio tracer used; might be sensitive to myelin content in cortex.	Limited human pathological validation; has not been extensively applied in multi-centre studies; difficulty in fabrication and timely transport of radiotracers; absolute quantification requires blood sampling.

Details of advanced imaging biomarkers currently used in clinical trials for people with progressive multiple sclerosis and included in consensus recommendations to quantify CNS compartmentalised inflammation (particularly the presence of chronic active lesions) or myelination status. [50,74]

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Abbreviations

EDSS= Expanded Disability Status Scale
9HPT=9-hole peg test
CDP=Confirmed disability progression
PBVC=Percentage brain volume change
T25FW=Timed 25 foot walk
SF36=Physical Component Summary score of the Medical Outcomes Study 36-Item Short-Form Health Survey
PRIMUS=Patient Reported Indices in Multiple Sclerosis
UFIS=Unidimensional Fatigue Impact Scale
MSWS-12=Multiple Sclerosis Walking Scale
ARR=Annualised relapse rate
MSIS-20=Multiple Sclerosis Impact Scale-29
FSS=Functional system score
SDMT=Symbol digit modalities test
CGI=Clinician-assessed clinical global impression score
SGI=Clinical global impression assessed by subject score
MSQoL-54
CAREQoL-MS
PASAT-3=Paced Auditory Serial Addition Test–3 [PASAT-3]).
SQOL-physical health
EQ-VAS=Health State Visual Analogue Scale

MFIS=Modified Fatigue Impact Scale
RNFL=Retinal nerve fibre layer
LCVA=Low contrast visual acuity
MAF=Multidimensional assessment of fatigue scale
MTR=Magnetization transfer ratio
FA=Fractional anisotropy
MWF=Myelin water fraction
OCT=Optical coherence tomography
VEP=Visual evoked potentials
MSFC=Multiple sclerosis functional composite
BICAMS=Brief International Cognitive Assessment for MS
NfL=Neurofilament light chain
BPF=Brain parenchymal fraction
BDI=Becks Depression Inventory
CUALs=Combined Unique Active Lesions
OWAT=Owatonna Cognitive Behavioural Test
NEDA=No evidence of disease activity
COWAT=Controlled Oral Word Association Test
CVLT-II= California Verbal Learning Test-II
Modified Rankin scale (mRS)
EQ-5D-5L=EuroQoL Health Related Quality of Life - 5 Dimensions - 5 Levels scores
Chi3L1=Chitinase-3 like protein 1
NFI-MS=Neurological Fatigue Index-Multiple Sclerosis
WPAI-GH=Work Productivity and Activity Impairment Questionnaire
FSMC=Fatigue Scale for Motor and Cognitive Functions
BRB-N=Brief Repeatable Battery of Neuropsychological Tests
HADS=Hospital Anxiety and Depression Scale
BDI-II=Beck Depression Inventory-revised
PDQ=Perceived Deficits Questionnaire
FAMS=Functional Assessment of Multiple Sclerosis
ORS=Overall Response Score
MEP=Motor evoked potential
SEP=Sensory evoked potential

BSAEP=Brainstem auditory evoked potential
CSRI=Client Services Receipt Inventory
6MWT=6-minute walk test