	Intervention	Proposed mechanism	N (active *vs* placebo, unless stated); ratio	Duration, years	Pre-trial progression, months	Multiple sclerosis duration (mean or progressive), years	Participants with PPMS *vs* SPMS, n (%)	Age: inclusion criteria (mean), years	Sex, n female (%)	EDSS entry range (mean)	Participants with baseline gadolinium-enhancing lesions¶, n/N (%)	Primary outcome (confirmation time); primary result
Phase 3 trials												
INFORMS 2016 (NCT00731692)	Fingolimod 0·5 mg daily	Oral sphingosine 1-phosphate receptor modulator; induced lymphopenia via sequestering of lymphocytes in lymph nodes	823 (336 *vs* 487); 1:1·4	3	≥12	2–10 (6)	823 (100%) PPMS	25–65 (49)	398 (48%)	3·5–6·0 (4·67)	107/820 (13%)	Time to composite of EDSS, T25FW, or 9HPT CDP (3 months); HR 0·95 (77·2% *vs* 80·3%, p=0·54)
MS-SPI 2016 (EudraCT:2013-002113-35)	High-dose biotin (MD1003) 100 mg three times daily	Activator of carboxylases, which might promote myelin repair and neuroprotection via enhanced energy production	154 (103 *vs* 51); 2:1	1	24	16	55 (36%) PPMS; 99 (64%) SPMS	18–75 (51)	88 (54%)	4·5–7·0 (6·1)	Not reported	Proportion of patients with disability improvement on EDSS at month 9 (month 12); 13 (13%) of treated patients *vs* none of placebo group (p=0·005)*
ORATORIO 2017 (NCT01247324 and NCT01412333)	Ocrelizumab 600 mg intravenously every 6 months	Humanised monoclonal antibody that selectively depletes CD20-expressing B cells	732 (488 *vs* 244); 2:1	≥2 (event-driven)†	≥12	<15 for EDSS>5·0, <10 for EDSS≤5·0 (6)	732 (100%) PPMS	18–55 (45)	361 (49%)	3·0–6·5 (4·7)	193/727 (27%)	Time to EDSS CDP (3 months); HR 0·76 (160 [33%] vs 96 [39%], p=0·03)*
PROMESS 2017 (NCT00241254)	Cyclophosphamide 750 mg/m^2 intravenously versus methylprednisolone 1 g **every 4 weeks** in year 1 every 8 weeks in year 2	A CNS penetrant nitrogen mustard alkylating agent, inducing lymphopenia	138 (72 cyclophosphamide *vs* 66 methylprednisolone); 1:1	2	12	13 (2)	138 (100%) SPMS	18–65 (48)	90 (65%)	4·0–6·5 (median 5)	Not reported	Time to EDSS CDP (16 weeks); adjusted HR 0·61 (95% CI 0·31–1·22), p=0·16
ASCEND 2018 (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 (5)	887 (100%) SPMS	18–58 (47)	550 (62%)	3·0–6·5 (median 6·0)	210/884 (24%)	Time to composite of EDSS, T25FW, or 9HPT CDP (6 months); OR 0·86 (195 [44%] *vs* 214 [48%], p=0·29)
EXPAND 2018 (NCT01665144)	Siponimod 2 mg daily	Selective inhibitor of sphingosine-1-phosphate	1651 (1105 *vs* 546); 2:1	<3 (event-driven)†	24	17 (4)	1651 (100%) SPMS	18–60 (48)	992 (60%)	3·0–6·5 (5·4)	351/1599 (22%)	Time to EDSS CDP (3 months); HR 0·79 (288 [26%] *vs* 173 [32%], p=0·013)*

		receptors 1 and 5; induces lymphopenia via sequester lymphocytes in lymph nodes										
SPI-2 2020 (NCT02936037)	High-dose biotin (MD1003) 100 mg three times daily	Activator of carboxylases, which might promote myelin repair and neuroprotection via enhanced energy production	642 (326 *vs* 316); 1:1	1	24	13 (from diagnosis)	227 (35%) PPMS *vs* 415 (65%) SPMS	18–75 (53)	345 (54%)	3·5–6·5 (5·4)	33/642 (5%)	Proportion of patients with disability improvement on EDSS or T25FWat month 12 (month 15); OR 1·35 (39 [12%] *vs* 29 [9%], p=0·31)
NCT01433497, 2022	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; inhibitor of microglia, macrophage, and mast cell activity	611 (200 masitinib 4·5 *vs* 101; 203 masitinib 6·0 *vs* 107); 2:1	2	24	9 (from diagnosis)	251 (41%) PPMS *vs* 360 (59%) non-active SPMS	18–75 (49)	316 (56%)	2·0–6·0 (5·3)	Not reported	Overall EDSS change from baseline week 12 in the masitinib 4·5 mg/kg per day *vs* placebo cohort (week 96); δEDSS 0·001 in 4·5 mg/kg per day group *vs* 0·098 in placebo, ΔLSM −0·097 (p=0·026)‡
Phase 2 trials [Prod: could be a separate table if that's any help]												
Tcelna presented 2016 (not published; NCT01684761)	Two annual courses of five subcutaneous Tcelna vaccine doses each year (at 0, 4, 8, 12, and 24 weeks)	An autologous pool of myelin reactive T cells expanded ex vivo	183	2	Not reported	Not reported	183 (100%) SPMS	18–60 [mean not reported]	Not reported	3·0–6·0 mean not reported	Not reported	Whole-brain atrophy; [A: can rate be omitted, or do you mean a decline per unit of time?] no significant benefit was reported [A: where, if results are not published?]
Spain et al 2017, NCT0118 8811	Lipoic acid 1200 mg daily	Antioxidant with multiple biological functions, including free-radical scavenging, metallic ion chelation, regeneration of intracellular glutathione, and repair of oxidative damage to macromolecules	51 (27 *vs* 24); 1:1	2	Not reported	30	51 (100%) SPMS	40–70 (59)	31 (61%)	Unlimited (5·8)	Not reported	Whole-brain atrophy; [A: can rate be omitted?] difference in atrophy 0·44%/year (–0·21% *vs* –0·65%, p=0·002 68% relative reduction*
ReBUILD 2017, NCT0204 0298	Clemastine fumarate 5·36 mg twice daily	First-generation antihistamine capable of inducing oligodendrocyte differentiation and myelination due to off-target antimuscarinic effect	50 (crossover trial); 1:1	0·5	NA	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 visual evol potential during treatment; delay 1·7 ms/eye (p=0·0048)*
NCT02228213 presented 2017 (not published)	MIS416 500 µg intravenously once weekly	Microparticulate immune response modifier targeting myeloid cells	93 (1:1)	1	Not reported	Not reported	93 (100%) SPMS	18–70 (mean not reported)	Not reported	3·0–6·5 (mean not reported)	Not reported	Change in neuromuscular function (multiple sclerosis functional composite, SDMT, Sloan low-contrast visual acuity, 6 min walk test)

Commented [NR1]: Thanks - re: atrophy rate - yes checking the main text we talk about "atrophy", rather than "atrophy rate" - so I have changed all these to "atrophy" for consistency. But whenever we are referring to atrophy, we are describing a change in volume over a unit of time - generally %change/year. We could perhaps include this in the legend if you felt it was required? Otherwise happy to leave it simply as "atrophy" as I think the readership will generally understand this term.

Commented [VL2]: Author name

Commented [VL3]: Please keep atrophy as refers to decline per unit time

INSPIRE 2017 (terminated by sponsor; 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 inhibiting nuclear factor κ B signalling	58; 1:1	2	Not reported	Not reported	58 (100%) SPMS	18–58 **(mean not reported)**	345 (54%)	3·0–6·5 **(mean not reported)**	10/58 (17%)	Time to composite of EDSS, T25FW, or 9HPT CDP (6 months)
SPRINT-MS 2018 (NCT01982942)	Ibudilast 100 mg daily	Inhibits phosphodiesterases, macrophage migration inhibitory factor, and toll-like receptor 4	255 (129 *vs* 126); 1:1	2	24	10	134 (53%) PPMS *vs* 121 (47%) SPMS	21–65 (56)	136 (53%)	3·0–6·5 (6·0)	·· **[A: NA? Unknown?]**	Whole-brain atrophy; difference of 0·0009/year (–0·0010 ibudilast *vs* –0·0019 placebo, p=0·04), 48% relative reduction
Tourbah et al 2018 (NCT02220244)	High-dose biotin (MD1003) 100 mg three times daily	Activator of carboxylases, which might promote myelin repair and neuroprotection via enhanced energy production	93 (65 *vs* 28); 2:1	0·5	·· **[A: NA? Unknown?]**	12	Worsening optic neuropathy; 34 (22%) SPMS *vs* 59 (63%) RRMS§	18–75 (41)	50 (54%)	·· **[A: NA? Unknown?]**	·· **[A: NA? Unknown?]**	Mean absolute change from baseline of best-corrected Logarithm of the Minimu Angle of Resolution visual acuity at 100% contrast in worse eye (month 6); mean difference –0·01983 (+3·1 *vs* +1·8 letters p=0·66
FLUOX-PMS 2019 (EudraCT: 2011-003775-11)	Fluoxetine 20 mg 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	·· **[A: NA? Unknown?]**	13	77 (58%) PPMS *vs* 55 (42%) SPMS	25–65 (53)	61 (45%)	3·0–6·5 (5·2)	·· **[A: NA? Unknown?]**	Time to T25FW or 9HPT CDP (3 months), HR 1·25 (95% CI 0·79–2·49)
SYNERGY 2019 (NCT01864148)	Opicinumab 3 mg/kg, 10 mg/kg, 30 mg/kg, or 100 mg/kg intravenously 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	·· **[A: NA? Unknown?]**	8	330 (79%) RRMS *vs* 88 (21%) active SPMS¶	18–58 (40)	277 (66%)	2·0–6·0 **(mean not reported)**	180/415 (43%)	Percentage with confirmed disability improvement: at least 1·0 **point** decrease in EDSS or at least 15% improvement in T25FW, 9HPT, or PASAT-3 (3 months); n difference in disability improvement wit 3 mg/kg (OR 0·98, p=0·96) or 100 mg/kg doses (OR 0·98, p=0·96), some evidence improvement with 10 mg/kg (OR 1·79, p=0·064) and 30 mg/kg doses (OR 2·06, p=0·022)*
IPPoMS 2020 (NCT00950248)	Idebenone 2250 mg daily	Synthetic quinone similar to coenzyme Q10; potentially promotes mitochondrial function	73 (38 *vs* 35); 1:1	2	·· **[A: NA? Unknown?]**	13	73 (100%) PPMS	18–65 (56)	34 (47%)	1·0–7·0 (3·2)	··**[A: NA? Unknown?]**	Change in CombiWISE||; treatment difference 0·15 (p=0·74)
MS-SMART 2020 (NCT01910259)	Amiloride 5 mg, fluoxetine 20 mg, or riluzole 50 mg daily	Amiloride: acid-sensing ion channel blockade; reduces neuronal sodium and calcium influx. Fluoxetine: selective serotonin-reuptake inhibitor; increased release of brain-	445 (111 amiloride *vs* 111 fluoxetine *vs* 111 riluzole *vs* 112	2	24	21 (6)	445 (100%) SPMS	25–65 (56)	298 (67%)	4·0–6·5 (6·0)	·· **[A: NA? Unknown?]**	Whole-brain atrophy; **[A: is "rate" needed?]** adjusted mean difference in atrophy *vs* placebo 0% (amiloride, p=0·99), –0·1% (fluoxetine, p=0·86), –0·1% (riluzole, p=0·77)

Commented [NR4]: Wherever a cell is left blank, it is because this data is not available. In some trials, it is because the data was not acquired (e.g. gadolinium enhanced imaging was not obtained at baseline); in other trials, it is because the data was acquired but not reported (e.g. for trials that have been presented but not published, available data is limited). I would suggest ".." With an explanation in the legend is better than repeating "not reported" regularly throughout the table?

Commented [NR5]: Yes you are correct its action could be described as "disinhibiting" remyelination - but we felt this double-negative terminology might be less clear than simply stating that it "promotes remyelination"

		derived neurotrophic factor from astrocytes and stimulation of astrocytic glycogenolysis. Riluzole: reduces glutamate release and antagonises voltage-dependent sodium channels.	placebo); 1:1:1:1									
ARPEGGIO 2020, NCT02284568	Laquinimod 0·6 mg or 1·5 mg	Small molecule immunomodulator; reduces 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%)	3·0–6·5 (4·5)	58 16%)	Whole-brain atrophy; adjusted mean difference 0·016% (–0.454% laquinimod *vs* 0·438% placebo, p=0·90)
Petrou et al 2020, **[A: is this the trial name, or do you mean "Petrou and colleagues?]** (NCT02166021)	MSC intrathecally or intravenously	Proposed immunomodulatory and neurotrophic effects	48 (16 intrathecal *vs* 16 intravenous *vs* 16 placebo); 1:1:1, crossover for second cycle after 6 months	1	·· **[A: NA? Unknown?]**	3	7 (15%) PPMS *vs* 41 (85%) SPMS	<65 (48)	20 (42%)	3·0–6·5 (5·9)	·· **[A: NA? Unknown?]**	Differences in EDSS score change: proportion with treatment failure, ie, increase in EDSS or deterioration in any FSS (6 and 12 months); two (7%) with treatment failure in MSC-IT, three (10%) in MSC-IV (p=0·0003), and 13 (42%) in placebo (p=0·0008); nine (31%) with FSS deterioration in MSC-IT, eight (28%) in MSC-IV (p=0·0002), and 23 (77%) in placebo (p=0·0004)
FUMAPMS 2021 (NCT02959658)	Dimethyl fumarate 240 mg daily	Immunomodulatory and neuroprotective properties by promoting nuclear factor erythroid-derived 2 pathway and inhibiting nuclear factor κ B signalling	54 (27 *vs* 27); 1:1	1	12	14	54 (100%) PPMS	18–65 (55)	21 (39%)	≤6·5 **(4.0)**	13% (n not reported)	Change in CSF neurofilament light chain 48 weeks); treatment effect +99 ng/L (95 CI −291·8 to 490·4 ng/L, p=0·61), +35 DMF *vs* −73 placebo (p=0·61)
RADIUS-P 2021 (not published; NCT03737812)	Elezanumab 400 mg or 1800 mg intravenously every 4 weeks	Monoclonal antibody to repulsive guidance molecule A, 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	·· **[A: NA? Unknown?]**	·· **[A: NA? Unknown?]**	59 (48%) PPMS *vs* 64 (52%) SPMS	·· **[A: NA? Unknown?]**	59 (48%)	Not reported	·· **[A: NA? Unknown?]**	Mean Overall Response Score (EDSS, T25FW, dominant or non-dominant 9HPT) from baseline (week 52); least squares mean difference from placebo 400 mg –0·01 (95% CI –0·48 to 0·46), 1800 mg 0·10 (–0·36 to 0·56)
Koch et al 2021, NCT02308137	Domperidone 10 mg four times daily	D2 receptor antagonist, increasing serum prolactin, which might promote remyelination	110 (single-arm, Simon two-stage design)	1	12	22	62 (100%) SPMS	18–60 (53)	47 (76%)	4·0–6·5 (6·1)	··**[A: NA? Unknown?]**	Proportion with more than 20% worsening of T25FW compared with baseline (12 months); 22 (35%) had worsening of T25FW (higher than the futility threshold)
Koch et al 2021, NCT02913157	Hydroxychloroquine 200 mg twice daily	Reduces the activation of human microglia and protects	49 (single-arm, Simon	1·5	·· **[A: NA?**	10	35 (100%) PPMS	18–65 (56)	13 (37%)	4·0–6·5 (5·6)	·· **[A: NA?**	Proportion with more than 20% worsening of T25FW compared with baseline (12

Commented [NR6]: Most of these trials have a specific name - which we have used together with the NCT number to identify them. Where there is not a specified trial name, I have put the first author's surname instead, and added et al - as this seems the best alternative? Otherwise we could just have the NCT only for unnamed trials?

		against experimental neurotoxicity	two-stage design)		Unknown?]						Unknown?]	months); eight (23%) had worsening of T25FW (lower than futility threshold)*
Rust et al 2021, NCT00799890	Epigallocatechin gallate 1200 mg daily	A polyphenolic green tea catechin with anti-inflammatory and neuroprotective properties	61 (30 *vs* 31); 1:1	3, 1 open-label extension	5·8	10	23 (38%) PPMS *vs* 38 (62%) SPMS	18–65 (49)	27 (44%)	3·0–8·0 (5·4)	·· [A: NA? Unknown?]	Whole-brain atrophy; 0·0092 *vs* 0·0078 (p=0·67)
MESEMS 2021, NCT01606215	Autologous MSC: single intravenous infusion	Proposed immunomodulatory and neurotrophic effects	144 (69 early treatment *vs* 75 early placebo and delayed treatment); 1:1	1	·· A: NA? Unknown?]	7	94 (65%) active RRMS *vs* 33 (23%) active SPMS *vs* 17 (12%) active PPMS	18–50 (39)	87 (60%)	2·5–6·5 (4·0)	61 (42%)	Total number of gadolinium-enhancing lesions (24 weeks); 1·16 for early MSC group *vs* 1·24 for early placebo group (RR 0·94, p=0·78)
NCT03355365 presented 2023 (not published)	Autologous MSC: six intravenous infusions spaced by 2-month intervals	Proposed immunomodulatory and neurotrophic effects	51 (24 *vs* 27); 1:1, crossover after 1 year	2	·· [A: NA? Unknown?]	·· [A: NA? Unknown?]	·· [A: NA? Unknown?]	·· [A: NA? Unknown?]	·· [A: NA? Unknown?]	3·0–6·5 (mean not reported)	·· [A: NA? Unknown?]	Improvement in EDSS-plus—EDSS, T25FW, or 9HPT (1 year); no significant differences reported in the primary outcome [A: reported where?]
CogEx 2023, NCT03679468	Cognitive rehabilitation and aerobic exercise versus cognitive rehabilitation (and exercise-sham) versus exercise (and cognitive rehabilitation-sham) versus exercise-sham and cognitive rehabilitation-sham	Postulated that aerobic exercise might 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 *vs* 227 (73%) SPMS	25–65 (53)	194 (62%)	<7·0 (6·0)	·· [A: NA? Unknown?]	SDMT correct responses (12 weeks); no significant differences; compared with t double-sham group, the mean differenc SDMT was –1·30 (95% CI –3·75 to 1·16) f cognitive rehabilitation plus exercise, –2 (–5·23 to –0·33) for sham-cognitive rehabilitation plus exercise, and –0·71 (– 3·11 to 1·70) for cognitive rehabilitation sham-exercise
EMBOLD press-release 2023 (not published), NCT03283826	ATA188 Epstein-Barr virus-directed allogenic cytotoxic T lymphocytes	Targets and depletes Epstein–Barr virus-infected B cells	103; 1:1 [A: should there be a second number if there were two groups?]	1	·· [A: NA? Unknown?]	·· [A: NA? Unknown?]	PPMS/SPMS (non-active) [A: unclear what this denotes. Should there be numbers?]	18–65 (··)	[A: missing data]	3·0–6·5 (mean not reported)	·· [A: NA? Unknown?]	Proportion with EDSS confirmed improvement (12 months); a press-release has stated the trial did not meet the primary endpoint with 6% CDI for ATA188 and 16% CDI for placebo. [A: if these data have been reported only in a press relea so far, please clarify for readers, eg sho we add "according to a press release" here and "unpublished" in the first column?]

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).

Commented [NR7]: The primary analysis result was reported at a conference in 2023, but the publication is awaited. This is the reference:

1. Roche M, Malin M, Stark J, et al. Efficacy of Intrathecal Mesenchymal Stem Cell-Neural Progenitor Therapy in Progressive MS: Results from a Phase II Clinical Trial. Presented at: 2023 AAN Annual Meeting; April 22-27; Boston, MA. Abstract 005. MS Clinical Trails and Therapeutics session.

Commented [NR8]: This data is not currently available - press release only

Commented [NR9]: This data is not currently available - press release only

Commented [NR10]: Yes agreed. Amended

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. ℗ 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. **[A: correct that no other trials of potentially remyelinating therapies have been done in people with RRMS or are there additional criteria for including this study that could be explained?]** ¶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 1: **Randomised controlled trials in progressive multiple sclerosis completed since 2014** **[A1: please check this column carefully as the data were presented in an unclear way and I want to be sure they're still correctly presented, thanks]**

Commented [NR11]: I've added further details that this trial specific recruited patients with chronic optic neuritis. This is explained more fully in the main text - I've directed readers to this).

	Intervention	Proposed mechanism	N (active:placebo ratio, unless stated)	Estimated year of completion	Trial duration, years	PPMS or SPMS	Entry EDSS	Age, years	Primary outcome (confirmation time)
Phase 3									
MS-STAT2, NCT03387670	Simvastatin 80 mg once daily	Hydroxymethylglutaryl-CoA inhibitor; cholesterol-independent (direct modulation of vascular endothelial and neuroglial function) and cholesterol-dependent pathways (modifying comorbidity) might be important	964 (1:1)	2024	3–4·5	SPMS	4·0–6·5	25–65	Time to EDSS CDP (6 months)
PERSEUS, NCT04458051	Tolebrutinib 60 mg 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 (6 months)
HERCULES, NCT04411641	Tolebrutinib 60 mg once daily	BTK inhibitor, suppressing B-cell and microglial activity	1290 (1:1)	2024	2–4	Non-relapsing SPMS	3·0–6·5	18–60	Time to EDSS CDP (6 months)
MAXIMS, NCT05441488	Masitinib 4·5 mg/kg per day, orally twice daily	Oral tyrosine-kinase inhibitor; inhibitor of microglia, macrophage, and mast cell activity	800 (1:1)	2025	2	Non-relapsing SPMS or PPMS	3·0–6·0	18–60	Time to EDSS CDP (3 months)
FENtrepid, NCT04544449	Fenebrutinib 200 mg twice daily *vs* ocrelizumab 600 mg intravenously 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, T25FW, or 9HPT CDP (3 months)
O'HAND, NCT04035005	Ocrelizumab 600 mg IV every 6 months	Humanised monoclonal antibody that selectively depletes CD20-expressing B cells	1000 (1:1)	2028	2	PPMS	3·0–8·0	18–65	Time to 9HPT CDP (3 months)
DanNORMS, NCT04688788	Rituximab 1000 mg intravenously every 6 months *vs* ocrelizumab 600 mg intravenously every 6 months	Rituximab: chimeric (mouse or human) anti-CD20 monoclonal antibody; ocrelizumab as above.	594 (2:1)	2028	2	RRMS, active SPMS, active PPMS*	≤6·5	18–65	Proportion without new or enlarging T2 white matter lesions
OCTOPUS, phase 2 and 3 (multiarm, multistage trial) ISRCTN14048364	Metformin 500 mg twice daily, increased to 1000 mg twice daily as tolerated; α-lipoic acid (R,S-enantiomer—R,S-α-lipoic acid) 600 mg once daily, increased to 600 mg twice daily as tolerated	Metformin activates AMPK via multiple intracellular pathways. It promotes oligodendrocyte progenitor differentiation via AMPK-dependent mechanisms. R-α-lipoic acid is a mitochondrial antioxidant. It might have additional anti-inflammatory effects via inhibition of nuclear factor-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	2028	Stage 1: 2 years; stage 2: continued for up	PPMS or SPMS	4·0–8·0	25–70	Stage 1: whole-brain atrophy; stage 2: time to EDSS-plus CDP (6 months; EDSS, T25FW, or 9HPT)

Commented [NR12]: As above - yes I think rate is helpful to be clear that we are talking about a longitudinal % change in brain volume rather than a cross-sectional measure of brain atrophy

			continues to stage 2		to 5 years				
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 antithymocyte 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)
Phase 2									
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
CHARIOT, NCT04695080	Cladribine 3·5mg/kg in two treatment courses 12 months apart	Purine analogue; pulsed selective depletion of B to T lymphocytes	200 (1:1)	2024	2	Advanced progressive multiple sclerosis	6·5–8·5	≥18	9HPT speed (24 months); proportion who did not deteriorate on 9HPT (24 months)
CALLIPER, NCT05054140	IMU-838 vidofludimus calcium 45 mg daily	Dihydroorotate dehydrogenase inhibition; limits lymphocyte proliferation via pyrimidine depletion	450 (1:1)	2024	2+8 open-label extension	PPMS or SPMS	3·0–6·5	18–65	Whole-brain atrophy
LAPMS, NCT03161028	Lipoic acid 1200 mg 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 or SPMS	3·0–6·5	18–70	T25FW change from baseline (year 2)
[A: correct no trial name?] NCT05013463	Hydroxychloroquine 200 mg twice daily and indapamide 2·5 mg daily	Hydroxychloroquine: reduces the activation of human microglia and protects against experimental neurotoxicity; indapamide: thiazide-like diuretic with proposed antioxidant and neuroprotective properties in vitro	35 (single-arm Simon two-stage design)	2024	1·5	SPMS	4·0–6·5	18–60	T25FW change (6 months to 18 months)
NACPMS, NCT05122559	N-acetyl cysteine 1200 mg three times daily	Precursor to the antioxidant glutathione	98 (1:1)	2025	1·25	PPMS or SPMS	3·0–7·0	40–70	Whole-brain, thalamic, and spinal cord atrophy
[A: correct no trial name?] NCT05630547	SAR443820	CNS-penetrant small molecule inhibitor of receptor-interacting protein kinase 1, which regulates inflammatory responses in microglial and astrocytes	168 (1:1)	2025	2	PPMS, SPMS, RRMS	2·0–6·0	18–60	Change in serum neurofilament light chain from baseline (part A: week 48, part B: week 96)

Commented [VL13]: Moved from table 1 to table 2 as trial appears to be ongoing as of 2022 and no further updates thereafter

Commented [VL14]: 2019 according to clinicaltrials.gov, but trial still ongoing as of 2022 as per https://doi.org/10.1016/j.msard.2022.103782

Commented [NR15]: Correct

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MACSiMiSE-BRAIN, NCT05893225	Metformin 850 mg orally twice to three times a day	Metformin activates AMPK via multiple intracellular pathways. It promotes oligodendrocyte progenitor differentiation via AMPK-dependent mechanisms. R-α-lipoic acid is a mitochondrial antioxidant. It might have additional anti-inflammatory effects via inhibition of nuclear factor-κB, with reduced lymphocyte activity and toll-like receptor gene expression.	120 (1:1)	2026	2	Non-active PPMS or SPMS on stable or no disease-modifying therapy	2·0–6·5	18–70	T25FW change from baseline, continuous variable
CLASP-MS, NCT05961644	Cladribine 1·8 mg/kg subcutaneously over six visits every 5–6 weeks for 6 months	Metformin activates AMPK via multiple intracellular pathways. It promotes oligodendrocyte progenitor differentiation via AMPK-dependent mechanisms. R-α-lipoic acid is a mitochondrial antioxidant. It might have additional anti-inflammatory effects via inhibition of nuclear factor-κB, with reduced lymphocyte activity and toll-like receptor gene expression.	118 (1:1)	2027	2	Non-active SPMS	3·5–7·5	30–65	Whole-brain atrophy
NORSEMAN, NCT05740722	Nicotinamide riboside, a nicotinamide adenine dinucleotide precursor	Increasing neuronal nicotinamide adenine dinucleotide is proposed to 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
HCQPET, EUCTR2022-003170-23-FI	Hydroxychloroquine 200 mg twice daily	Hydroxychloroquine: reduces the activation of human microglia and protects against experimental neurotoxicity; indapamide: thiazide-like diuretic with proposed antioxidant and neuroprotective properties in vitro	30 (1:1)	·· [A: no expected end date?]	1	PPMS or non-active SPMS	3·5–7·0	35–65	Change in supratentorial white matter PET 18 kDa translocator protein signal from baseline (end of study)

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 2: **Ongoing randomised controlled trials in progressive multiple sclerosis**

Commented [NR17]: Not available

	Description	Clinically meaningful change	Proportion with CDP (6 months) in 2-year trials	Comment	Examples
Clinician-assessed outcomes					
EDSS	A clinician-rated ordinal scale ranging from 0 (no symptoms or signs) to 10 (death due to multiple sclerosis).	A 0·5 or 1·0 point increase, depending on the baseline disability score	13–29%	In trials of progressive multiple sclerosis, EDSS primarily reflects lower limb function and recent publications have highlighted potential issues with reliability; it is, however, accepted by regulatory authorities.	EXPAND and ORATORIO: positive primary outcomes have led to the licensing of siponimod and ocrelizumab.
Performance-based outcomes					
Timed 9HPT	An upper limb measure assessing the time required to place nine pegs in a board and remove them again, repeated twice with each hand. The maximum time per trial is 300 s.	≥20% worsening from baseline	8–12%	Allows the inclusion of non-ambulant people in trials, a previously neglected group. There is not a consensus around analytical approaches (average of both hands *vs* either hand *vs* dominant hand to define 20% change); there are greater short-term fluctuations compared with EDSS.	Primary outcome for the ongoing O'HAND and CHARIOT-MS (time to 20% CDP in O'HAND, and continuous speed at 24 months in CHARIOT-MS). In ASCEND, natalizumab significantly delayed time to 20% CDP on 9HPT (secondary outcome).
T25FW	A lower limb measure assessing the time required to walk 25 feet. It is repeated twice and averaged. The maximum time per trial is 300 s.	≥20% worsening from baseline	25–32%	May show greater short-term fluctuations compared with EDSS.	ORATORIO: lower mean change in T25FW for ocrelizumab compared with placebo. EXPAND and ASCEND: no significant benefits on T25FW CDP.

SLCVA	Low-contrast letters, typically at 2·5% with either monocular or binocular vision, are read from standardised charts; the total number of correct letters determines the score (maximum 70).	≥7 point worsening from baseline	..	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 benefit with clemastine compared with placebo on SLCVA (2·5%, continuous variable).
SDMT	Participants decode rows of symbols into digits, using a key; total number of correct verbal responses in 90 s determines the score (maximum 110).	≥4 point worsening from baseline	31%*	Well validated and available in multiple languages; currently the preferred outcome to assess information processing speed.	EXPAND: post-hoc analysis suggested siponimod reduced the risk of SDMT CDP (HR 0·79, 95% CI 0·65–0·96). CogEx: SDMT used at 12 weeks (analysed as a continuous variable) as the primary outcome; no benefit was found for cognitive rehabilitation or aerobic exercise compared with placebo.
BVMT-R	Participants are shown six simple geometric shapes for 10 s, then must draw them immediately from memory (three consecutive attempts, maximum score 36).	Consensus yet to be established **[A: correct?]**	..	Reliable and valid across multiple languages; absence of consensus on clinically meaningful change limits time-to-event analysis.	EXPAND: post-hoc analysis found no significant difference between siponimod and placebo (BVMT-R as a continuous variable).
CVLT-2	Participants listen to a list of 16 words and are assessed by immediate verbal recall (five consecutive attempts, maximum score 80).	Consensus yet to be established **[A: correct?]**	..	As for BVMT-R, reliable and valid in multiple languages, but no consensus on clinically meaningful change.	FLUOX-PMS: secondary analyses found no significant difference with fluoxetine compared with placebo on CVLT-2 (consistent with the primary outcome).
Multicomponent outcomes					
EDSS-plus **[A: add a footnote**	Progression is typically defined as clinically significant worsening achieved on EDSS, T25FW, or 9HPT.	A 0·5 or 1·0 point increase on EDSS, or	30–54%	Higher event rates increase trial power, but multicomponent outcomes incorporate the measurement error of	ASCEND: natalizumab did not show significant benefit compared with placebo on the primary multicomponent outcome of

Commented [NR18]: Correct - there is no established consensus

Commented [NR19]: Yes

to say this is an example and that others exist? Can others be mentioned in the legend?]		≥20% worsening on either 9HPT or T25FW		each individual component; currently not accepted by regulatory authorities.	EDSS-plus, despite a positive secondary outcome on 9HPT alone. INFORMS: fingolimod did not show significant benefit compared with placebo on EDSS-plus or any of its subcomponents.
PROs					
MSIS-29	A multiple sclerosis-specific questionnaire; participants rate the impact of their multiple sclerosis during the previous 2 weeks on ordinal scales. 20 items relate to physical health and nine to psychological health, with higher scores indicating more severe impairment. (Version 1 scores from 1 to 5, version 2 from 1 to 4; hence maximum 145 for version 1 and 116 for version 2.)	Worsening of 8 points on the MSIS-29, or on its physical subscale (version 1)	~30%†	No current consensus regarding use in multiple sclerosis clinical trials; further data are required to establish clinically meaningful changes and further assess their validity, reliability, and responsiveness to interventions.	ASCEND and MS-SMART: consistent with the primary analyses, no significant differences were seen on MSIS-29 physical subscores. In EXPAND, siponimod reduced the risk of a 7·5 point increase by 21·8% (HR 0·78, 95% CI 0·64–0·95).
Multiple Sclerosis Walking Scale 12	A multiple sclerosis-specific questionnaire; participants rate the impact of their multiple sclerosis on lower limb function using ordinal scales. Higher scores indicate more severe impairment. (Version 1 scores from 1 to 5, version 2 reduces three items to 1 to 3; hence	Worsening of 8 points (version 1)	~30%†	No current consensus regarding use in multiple sclerosis clinical trials; further data are required to establish clinically meaningful changes and further assess their validity, reliability, and responsiveness to interventions.	EXPAND: post-hoc analyses found a −1·77 (−3·59 to 0·05) difference with siponimod compared with placebo; siponimod reduced risk of an 8 point increase by 24·5% (HR 0·75, 95% CI 0·62–0·92). INFORMS and ASCEND: neither fingolimod nor natalizumab showed significant benefit compared with placebo (consistent with the primary outcomes).

Commented [NR20]: This is the only multi-component outcome to be used in completed or ongoing trials in PMS - hence I think it is the only one to mention.

	maximum of 60 for version 1 and 54 for version 2.)				
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 (SD 10) corresponds to that of the general US population.	Worsening of 5 points (half an SD) on the physical and mental health summary scores (although not validated in multiple sclerosis cohorts)	..	No current consensus regarding use in multiple sclerosis clinical trials; further data are required to establish clinically meaningful changes and further assess their validity, reliability, and responsiveness to interventions.	ORATORIO: contrary to the primary outcome, ocrelizumab did not show significant benefits compared with placebo on the SF-36 physical summary score; similarly, in MS-SPI, biotin treatment was not associated with consistent benefits on SF-36 subscores compared with placebo, despite the positive primary outcome.
MSQOL-54	Based on the SF-36, but with 18 additional items more specific to multiple sclerosis-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).	Consensus yet to be established **[A: correct?]**	..	No current consensus regarding use in multiple sclerosis clinical trials; further data are required to establish clinically meaningful changes and further assess their validity, reliability, and responsiveness to interventions.	SPI-2: consistent with the primary outcome, an exploratory analysis found no significant differences between biotin and placebo on MSQOL-54 physical or mental health summary scores. Vermersch: contrary to the positive primary outcome, there were no significant differences between masitinib and placebo on either MSQOL-54 summary score.

Physician-assessed, performance-based, and patient-reported outcome measures commonly used in recent randomised controlled trials in progressive multiple sclerosis. For a fully referenced version of this table, see appendix 1 (pp 12–14). 9HPT=nine-hole peg test. BVMT-R=Revised Brief Visuospatial Memory Test. CDP=confirmed disability progression. CVLT-2=Californian Verbal Learning Test version 2. EDSS=Expanded Disability Status Scale. MSIS-29=Multiple Sclerosis Impact Scale 29. MSQoL-54=Multiple Sclerosis Quality of Life 54. PRO=patient-reported outcome. SDMT=symbol digit modality test. SF-36=Medical Outcomes Study 36-Item Short Form Health Survey. SLCVA=Sloan low-contrast visual acuity. T25FW=timed 25-foot walk. 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. **[A: in EXPAND? Are the other values in this column ranges from the trials named in the example column?**

Commented [NR21]: Yes

Can a note be added to explain this and why several other cells in the column are empty?] †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.

Table 3: **Key clinical outcome measures used in trials for progressive multiple sclerosis**

Commented [NR22]: Thanks - I've added a note.

The CDP data is often from the trials in the examples column, but not always, and the CDP data is often not reported in the main trial publication - it has usually been published in separate post-hoc analyses specifically looking at defining CDP rates. The appendix contains the references for each of these CDP figures - so I think we should direct readers to that if they wish to know the origin of the CDP figures.

	Signal source or measure	Pathology validation	Advantages	Disadvantages
Compartmentalised CNS inflammation—imaging chronic active lesions				
Paramagnetic rim lesions	Detection of iron accumulated in active microglia or macrophages at the rim of lesions via T2* or susceptibility weighted images, and quantitative susceptibility mapping	Human	Sequences available on clinical scanners; short acquisition (<5 min); published guidelines on reporting available	Longitudinal dynamics of paramagnetic rim lesion development and resolution remain unknown; limited data on response to treatment
Slowly expanding lesions	Automated pipelines apply deformation-based techniques to detect consistent concentric expansion of white matter lesions across coregistered longitudinal imaging	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 three timepoints; insufficient histological validation; overlap between slowly expanding and paramagnetic rim lesions at the lesion level is low—they might represent similar, but different, biological processes
PET	Several radiotracers with specificity to microglia are available, including those targeting translocator protein 18 kDa and cyclo-oxygenase-2	Animal, human	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.	Specificity of translocator protein 18 kDa signal to human activated microglia has been questioned—likely to represent microglial/macrophage density rather than activation state; limitations due to radiotracer production, cost, harmonisation of analytical methods, low spatial resolution, and physiological properties of different tracers
Myelin imaging techniques				

Magnetisation transfer ratio	Ratio representing exchange of macromolecule-bound and free protons	Animal, human	Ease of acquisition; short acquisition time; extensive experience already in clinical trials	Not completely specific to myelin; requires within-patient and multicentre calibration; susceptible to field inhomogeneity and other pathological processes, such as oedema, inflammation and axonal density.
Quantitative magnetisation transfer imaging	Quantitation of macromolecule-bound and free proton exchange	Animal, human	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 validation in multicentre studies **compared to MTR**
Diffusion tensor imaging	Water diffusion modelled in tensor with myelin-sensitive measures perpendicular to axons (fractional anisotropy, mean diffusivity, radial diffusivity)	Animal, human	Easily acquired, with established measurement values; some experience with multicentre implementation	Technically difficult to apply in multicentre fashion; not pathologically sensitive; some difficulty interpreting changes when crossing fibres are present
Myelin water imaging	Distribution of T2 relaxation from water trapped in myelin bilayers; myelin water fraction is derived from the short T2 component (myelin water) over total water content	Animal, human	Can be more specific for myelin than other techniques; sensitive to white matter demyelination and multiple sclerosis lesions	Long acquisition time and complex analysis; has not been extensively applied in multicentre studies
Direct visualisation of short transverse relaxation time component	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 multicentre studies; limited pathological validation

Quantitative susceptibility mapping	Acquires diamagnetic signal from myelin-related susceptibility	Animal, human	Fast acquisition time; images can be created by saving phase images during susceptibility weighted imaging or T2* acquisitions	Significant postprocessing required, which is not fully standardised; has not been extensively applied in multicentre studies
PET	Several radiotracers with specificity to myelin components or associated axonal components are available, including 1,4-bis(p-aminostyryl)-2-methoxy benzene, [(^{11}C)] 2-(4′-methylaminophenyl)-6-hydroxybenzothiazole, [(^{11}C)] Case Imaging Compound, and [(^{11}C)] N-methyl-4,4′-diaminostilbene	Animal, human	Might provide a more specific measure of myelin content compared to other techniques depending on the radiotracer used; might be sensitive to myelin content in the cortex	Little human pathological validation; has not been extensively applied in multicentre 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. For a fully referenced version of this table, see appendix 1 (pp 15–17).

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