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Novel multiple sclerosis drugs in the pipeline

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Introduction

Multiple sclerosis (MS) is an immune-mediated inflammatory disease of the central nervous system (CNS) affecting more than 2 million people worldwide. Patients with MS may develop clinical relapses and/or magnetic resonance imaging new lesions (disease activity) and relentless neurological disability independent of relapses (disease progression). The licenced disease-modifying therapies (DMTs) impact the natural history of MS, mostly by reducing disease activity; however, they have limited ability to prevent disease progression and cannot reverse CNS damage.

Drugs in development for the clinically isolated syndrome

The concept of preventing the conversion of clinically isolated syndrome (CIS) to MS using currently approved DMTs has evolved. According to the recently revised diagnostic criteria [1], MS can be diagnosed at a very early stage, which questions the translation of results from clinical trials undertaken so far to contemporary CIS populations. Interferon-β and glatiramer acetate are the only licenced DMTs for CIS; however, two phase III trials have shown that teriflunomide and cladribine can significantly decrease the risk of conversion of CIS to MS, providing benefits comparable or possibly superior to the ones from interferon-β and glatiramer acetate (Supporting information).

Drugs in development for relapsing-remitting multiple sclerosis

It is classically believed that, early in the course of the disease, pro-inflammatory T-cells are activated in the periphery, by as yet unidentified antigens, and subsequently cross the blood-

brain barrier secreting proinflammatory cytokines into the CNS.[2] The first DMTs developed for MS – interferon-β and glatiramer acetate – modulate the immune system on different levels including inhibition or stimulation of cytokines with pro- or anti-inflammatory activity. This DMT mechanism of action is being further investigated in two ongoing studies of a combined neuropeptide - EK-12 - and a monoclonal antibody - AIN457 - capable of promoting pro-inflammatory cytokine inhibition (Table 1). Other DMTs, such as fingolimod and natalizumab, act by decreasing the ability of T-cells to reach or cross the blood-brain barrier. Alemtuzumab, a monoclonal antibody directed against CD52, suppresses lymphocytes inducing long-lasting depletion of T-cells.

The cytokine modulation or blockade of T lymphocytes, however, has not always been successful in MS. New players and mechanisms of damage in the inflammatory process of MS have been pursued. B cells, for instance, are now regarded as important activators of pro-inflammatory T-cells. Several monoclonal antibodies targeting B cells by binding CD20 are under investigation. Rituximab was the first anti-CD20 monoclonal antibody showing significant reduction of relapses and gadolinium-enhancing lesions (GELs) in relapsing-remitting MS (RRMS).[3] Following the rituximab pilot study, ocrelizumab, a fully humanised anti-CD20 monoclonal antibody, was tested in two large phase III trials providing additional evidence of B-cell involvement in the pathophysiology of RRMS and leading to the Food and Drug Administration (FDA) approval of this drug in 2017. The phase III RE-FUND trial is underway to test the efficacy of rituximab over dimethyl fumarate in reducing the relapse rate in about 200 patients with RRMS. Other anti-CD20 monoclonal antibodies, such as ofatumumab and ublituximab, are being investigated in randomised clinical trials (Table 1). Bruton’s tyrosine kinase (BTK) is a Tec-family kinase essential for reprogramming the expression of genes that control B-cell survival and proliferation. Inhibition of BTK

results in blocks in B-cell development and impaired function of residual mature B cells. In a phase II trial, the BTK inhibitor evobrutinib was effective in decreasing the number of GELs in 267 patients with RRMS or active secondary progressive MS (SPMS) (Table 1).

Cell-based therapeutic strategies are linked to immune reconstitution or induction therapy, that is, the ability to induce immune reset and consequent long-lasting drug-free remission. Studies on autologous hematopoietic stem cell transplantation have shown effective immunomodulation in patients with active MS and the open-label randomised MIST study is currently comparing the efficacy of peripheral blood stem cell transplantation versus FDA approved standard of care in patients with active RRMS despite treatment with alternate approved therapy (NCT00273364). Animal studies have also shown that grafted mesenchymal stem cells can repair CNS lesions and induce recovery of damaged neurological functions. Currently, there are on-going phase II trials recruiting participants to explore dose, mode of administration, safety and efficacy of hematopoietic or mesenchymal stem cells. Induction therapy can also be achieved with alemtuzumab and cladribine, which are administered for a few days every 12 months over 2 years. The RAM-MS trial is recruiting patients to compare the efficacy of hematopoietic stem cell transplantation versus alemtuzumab (Table 1). Cladribine's FDA approval is pending, but the drug can be prescribed in Europe, Canada, and Australia.

Inflammation is not the only mechanism that current research in MS has addressed. There is evidence, for instance, that cerebral perfusion is altered in patients with MS contributing to tissue damage. Researchers are looking at the safety and efficacy of acetazolamide to improve cerebral perfusion in relapsing MS (NCT02466074). Other studies have focused on anti-viral therapies, such as the antiretroviral agent raltegravir (NCT01767701) or the

monoclonal antibody GNbAC1 (Table 1), based on evidence showing the involvement of the Human Endogenous Retrovirus in the pathogenesis of MS. Other studies, instead, have looked at the potential of T-cell immunotherapy or the protective role of helminth colonisation (Supportive information).

Remyelination is also being actively explored. An open-label study investigating the capability of domperidone to raise prolactin levels in patients with RRMS on DMTs is being pursued, based on the observation that prolactin enhances remyelination in animal models (NCT02493049). Some evidence of remyelination, as calculated by the mean changes in post-lesion magnetic transfer ratio (MTR) in GELs and Delta-MTR, come from a placebo-controlled trial that tested the drug GSK239512, a selective H3 receptor antagonist, as an add-on to interferon-β or glatiramer acetate (Table1). Clemastine, a first-generation antihistamine, thought to promote oligodendrocyte differentiation and myelination, improved the P100 latency delay on full-field, pattern-reversal, visual-evoked potentials, in a human optic nerve system. Another study - the phase 2 AFFINITY trial - is currently underway to clarify the remyelination role of the CD20 monoclonal antibody opicinumab in RRMS patients on DMTs (Table1).

Finally, combination treatment. There is one phase III study assessing the sphingosine-1-phosphate receptor 1 ponesimod versus placebo, in patients already on dimethyl fumarate (Table1).

Drugs in development for progressive multiple sclerosis

Delivering effective treatments in progressive MS is difficult. Many trials have been carried out and failed, for reasons not always attributable to drug inefficacy. [4,5] It is believed that the pathogenic mechanisms in the progressive stages are different from those in the relapsing phase, and that the currently available clinical outcomes are not sensitive enough to detect significant changes in a timely manner. However, post hoc analyses from clinical trials in progressive MS suggested that younger and less disabled patients with shorter disease duration and ongoing disease activity were likely to have a greater benefit from DMT treatment (Supporting information). This was confirmed in the two recent pivotal trials, ORATORIO and EXPAND, assessing ocrelizumab in primary progressive MS (PPMS) and siponimod in SPMS respectively. ORATORIO recruited patients with less than 10 or 15 years of disease duration, moderate disability and not older than 55 years of age. The trial was associated with a relative risk reduction of 24% of 12-week confirmed disability progression (primary outcome) versus placebo and has received FDA approval for PPMS in 2017. Siponimod was associated with a significant decrease risk of 3-month confirmed disability progression as compared with placebo (hazard ratio 0.79, 95% confidence interval [CI] 0.65–0.95; p=0.013), with the results being more relevant for younger patients with active disease.

The MS-SPI phase II trial addressed the effect of the vitamin biotin in inducing clinical improvement in 154 progressive MS patients. A total of 13 (12.6%; 95% CI 6.9%–20.6%) patients treated with biotin had a reduction in MS-related disability at month 9, confirmed at month 12, compared with none in the placebo arm. This study had some limitations, such as the absence of separate examining and treating physicians. The confirmatory phase III SPI-2 study is underway (Table2).

Another positive study was the phase II SPRINT-MS trial, which examined ibudilast in 255 patients with progressive MS. Ibudilast reduced the rate of brain atrophy by 48% compared to

placebo as measured by parenchymal brain fraction, warranting a phase III trial. Similarly, simvastatin was associated with significant reduction of the percentage of brain volume change in patients with SPMS in the placebo-controlled phase II trial MS-STAT and is now being investigated in a larger phase III study (Table2).

A small trial reporting promising results was the phase II study of lipoic acid in 51 patients with SPMS (Table2), which showed 68% reduction in the rate of brain atrophy in the active arm versus placebo. However, this trial had a small sample size and showed a near significant increase in the T2 lesion volume (p=0.058) in the lipoic acid arm, a potential confounder.

Conclusions

The past twenty-five years have seen the introduction of many treatments for RRMS, with increased efficacy and improved tolerability. Practice has now turned to investigate combination and sequencing strategies. Although the discovery of therapeutics for progressive MS has not been equally successful, ocrelizumab, the first DMT for PPMS, has been recently marketed, and siponimod has shown efficacy in SPMS. Research into novel treatments is ongoing, moving towards myelin repair and neuroprotection. Clinical trials have started to address disease improvement, rather than disease progression. Tens of agents with a variety of different mechanisms of action are now being investigated in proof-of-concept phase II studies. More than five phase III trials are ongoing in RRMS and a further three in progressive MS. The results of these studies will be available over the next five to ten years, and will undoubtedly change the future of the management of patients with MS, in all its forms.

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Drug	Mechanism of Action	Abbreviated Study Name NCT identifier	Duration	Participants	Comparator	Status	Primary Endpoint	Results
PHASE II TRIALS								
AIN457	Human antibody against interleukin-17A elaborated by T helper 17, exhibiting proinflammatory properties.	POC-MD [NCT01051817]	24 wks	73 RRMS	Placebo	Completed	CUAL	Not reported
Amiselimod (MT-1303)	Selective modulator of S1P1 receptors, which induce lymphocyte sequestration in lymph nodes avoiding lymphocytes to cross the BBB.	MOMENTUM [NCT01742052]	24 wks	415 RRMS	Placebo	Completed (Extension trial ongoing)	GELs	Positive
Ceralifimod (ONO-4641)	Selective modulator of S1P1 and S1P5 receptors, which induce lymphocyte sequestration in lymph nodes avoiding lymphocytes to cross the BBB. S1P5 modulation may be neuroprotective.	DreaMS	26 wks	407 RRMS	Placebo	Completed	GELs	Not reported
CHS-131 (INT-131)	Highly-selective PPAR-gamma agonist that crosses the BBB and exerts anti-inflammatory activity in the CNS	INT131 in Treatment-naïve RRMS [NCT02638038]	6 mts	228 RRMS	Placebo	Completed	GELs	Positive
Clemastine	First generation antihistamine capable of crossing the BBB and inducing oligodendrocyte differentiation and myelination	ReBUILD [NCT02040298]	150 dys	50 RRMS	Placebo	Completed	P100 latency	Positive
Evobrutinib (M2951)	Bruton's tyrosine kinase inhibitor which works by inhibiting the B-cell signalling pathway, limiting B-cell maturation.	M2951 in Ssbjects with relapsing MS [NCT02975349]	48 wks	267 - RRMS - active SPMS	- Placebo - Dimethyl Fumarate	Study active Not recruiting	GELs	N/A
Firategrast (SB-683699)	Oral monoclonal antibody α4β-integrin agonist with short half-life, which reduces trafficking of mononuclear white blood cells across the BBB.	Study of SB-683699 in RRMS [NCT00395317]	24 wks	343 RRMS	Placebo	Completed	GELs	Positive
GSK239512	Selective, orally bioavailable and brain penetrant H3 receptor antagonist/inverse agonist thought to promote remyelination	GSK239512 in RRMS [NCT01772199]	48 wks	131 RRMS	Placebo [patients must be on IFNβ-1a or GA]	Completed	- Mean post-lesion MTR GELs - Delta-MTR lesions	Positive
GNbAC1	Monoclonal antibody directed against the surface envelope protein of the HERV-W	CHANGE-MS [NCT02782858]	24 wks	270 RRMS	Placebo	Completed	- GELs	Negative, but MTR post hoc analyses showed possible remyelination properties
Mesenchymal stem cells	Mesenchymal stem cells, obtained by several sources, have anti-inflammatory, low immunogenicity, multipotency properties and can differentiate into neurons and glial.	MESCAMS [NCT02239393]	40 wks	40 (target) - RRMS - Active PMS	Placebo	Recruiting	Safety GELs	N/A
		STREAMS** [NCT01606215]	1 yr	19 - RRMS - Active/progressing PMS	Placebo	Completed	Safety GELs	Not reported
		MESEMS** [NCT01854957]	48 wks	20 - RRMS - Active PMS	Placebo	Unknown	Safety GELs	N/A

		Autologous Mesenchymal Stem Cell Transplantation in MS [NCT01377870]	12 mts	22 RRMS	Placebo	Completed	GELs Brain atrophy Severe relapses EDSS MSFC	Not reported
Opicinumab (Anti-LINGO-1 or BIIB033)	Human monoclonal antibody against leucine-rich repeat and immunoglobulin-like domain-containing protein 1 (LINGO-1), an oligodendrocyte differentiation and myelination suppressor, with possible remyelination/neuroprotection effects in the CNS.	SYNERGY [NCT01864148]	84 wks	412 - 326 RRMS - 86 SPMS	Placebo (patient must be on IFN β-1a)	Completed	Improvement of ≥1 of the following: EDSS T25FW 9HPT PASAT-3	Negative, but efficacy cannot be excluded (inverted U-shaped dose response)
		AFFINITY [NCT03222973]	72 wks	240 RRMS (target)	Placebo (patients must be on anti-inflammatory DMT)	Active	Improvement of composite score: EDSS T25FW 9HPT	N/A
Siponimod (BAF 312)	Selective modulator of S1P1 and S1P5 receptors, which induce lymphocyte sequestration in lymph nodes avoiding lymphocytes to cross the BBB. S1P5 modulation may be neuroprotective.	BOLD [NCT00879658]	6 mts	296 RRMS	Placebo	Completed	CUAL	Positive
Sunphenon Epigallocatechin-gallate (EGCg)	Polyphenol compound (from green tea leaves extract) with neuroprotective properties by acting as a radical scavenging system.	SuniMS [NCT00525668]	18 mts	120 RRMS	Placebo (patients must be on GA)	Completed	T2 lesions	Not reported
Tabalumab (LY2127399)	Selective fully human IgG4 monoclonal antibody with neutralising activity against BAFF, an essential survival factor for B cells.	A Study of Patients with Relapsing Remitting Multiple Sclerosis [NCT00882999]	48 wks	245 RRMS	Placebo	Completed	GELs	Not reported
VAY736	Defucosylated human IgG1 monoclonal antibody targeting the receptor for BAFF.	Effect of a Single Infusion of VAY736 on Disease Activity in Patients with RRMS [NCT02038049]	16 wks	8 RRMS	Placebo	Completed	GELs	Not reported
PHASE III TRIALS								
EK-12 (metenkefalin-tridecactide combined neuropeptide)	Tridecactide analogue of the adrenocorticotropic hormone. It has anti-inflammatory effects by downregulation of pro-inflammatory cytokines and upregulation of IL-10.	EK-12 in Patients with RRMS [NCT03283397]	144 wks	400 RRMS (target)	IFNβ-1a	Not yet recruiting	AAR	N/A
Hematopoietic Stem Cell Transplantation (AHSCT)	Immune-reconstitution is prompted by the AHSCT procedure, which depletes a broad spectrum of lymphoid and myeloid cells. These cells include adaptive immune cells (T cells and B cells) and innate immune cells (natural killer cells, dendritic cells, monocytes and granulocytes).	RAM-MS [NCT03477500]	96 wks	100 (target)	Alemtuzumab	Recruiting	NEDA	N/A
Laquinimod	A quinoline-3-carboxamide derivative molecule able to cross the BBB and modulate CNS innate immune system cells, such as astrocytes and	BRAVO [NCT00605215]	24 mts	1331 RRMS	- Placebo - IFNβ-1a	Completed	ARR	Negative
		ALLEGRO	24 mts	1106 RRMS	Placebo	Completed	ARR	Positive

	microglia. In addition, it may be neuroprotective by upregulation of BDNF.	[NCT00509145]						
		CONCERTO [NCT01707992]		2199 RRMS		Completed	EDSS	Negative
Ofatumumab	Subcutaneous anti-CD20 therapy fully human monoclonal antibody which appears to inhibit early-stage B lymphocyte activation.	*MIRROR [NCT01457924]	48wks	232 RRMS	Placebo	Completed	GELs	Positive
		ASCLEPIOS I [NCT02792218]	2.5 yrs	928 RRMS (target)	Teriflunomide	Study active Not recruiting	ARR	N/A
		ASCLEPIOS II [NCT02792231]	2.5 yrs	956 RRMS (target)	Teriflunomide	Study active Not recruiting	ARR	N/A
Ozanimod	Selective modulator of S1P1 and S1P5 receptors, which induce lymphocyte sequestration in lymph nodes avoiding lymphocytes to cross the BBB. S1P5 modulation may be neuroprotective.	*RADIANCE [A: NCT01628393]	24 wks	258 RRMS	Placebo	Completed	GELs	N/A
		[B: NCT02047734]	24yrs	1313 RRMS	IFNβ-1a	Completed	ARR	Positive
		SUNBEAM [NCT02294058]		1346 RRMS	IFNβ-1a	Completed	ARR	Positive
Ponesimod (ACT-128800)	Selective modulator of S1P1 receptors, which induce lymphocyte sequestration in lymph nodes avoiding lymphocytes to cross the BBB.	*Oral ponesimod in RRMS [NCT01006265]	24 wks	464 RRMS	Placebo	Completed	GELs	Positive
		OPTIMUM [NCT02425644]	108 wks	1100 RRMS (target)	Teriflunomide	Active. Not recruiting	ARR	N/A
		POINT [NCT02907177]	167 wks (max)	600 RRMS (target)	Placebo [patients must be on Dimethyl Fumarate]	Recruiting	ARR	N/A
Rituximab	Chimeric anti-CD20 antibody capable to inhibit B lymphocyte activation.	RIFUND-MS [NCT02746744]	2 yrs	200 RRMS (target)	Dimethyl fumarate	Recruiting	Freedom from relapse	N/A
Ublituximab (TG-1101)	Glycoengineered monoclonal antibody that targets a unique epitope on the B-lymphocyte CD20 antigen with high antibody-dependent cellular cytotoxicity activity. It inhibits B lymphocyte.	*TG1101-RMS201 [NCT03381170]	52 wks	48 RRMS	Placebo	Completed	B cell depletion	Positive
		ULTIMATE 1 [NCT03277261]	96 wks	440 RRMS (target)	Teriflunomide	Recruiting	ARR	N/A
		ULTIMATE 2 [NCT03277248]	96 wks	440 RRMS (target)	Teriflunomide	Recruiting	ARR	N/A

Table 1 Clinical trials in relapsing-remitting multiple sclerosis showing promising results or currently ongoing (source ClinicalTrials.gov, last accessed October 22, 2018).
Only double-blind randomised clinical trials with an efficacy primary endpoint have been included. AAR= annualised relapse rate. BAFF= B-cell activating factor belonging to the tumour necrosis factor family. BBB= blood–brain barrier. BDNF= brain-derived neurotrophic factor. CDP= confirmed disability progression. CNS= central nervous system. CUAL= Combined unique active lesions. DMT= disease-modifying therapy. EDSS= Expanded Disability Status Scale. GA= glatiramer acetate. GELs= gadolinium enhancing lesions. HERV-W= Human endogenous retrovirus-W (also known as multiple sclerosis-associate endogenous retrovirus). IFNβ= interferon beta. MSFC= multiple sclerosis functional composite. MTR= magnetic transfer ratio. N/A= not applicable. NCT= number clinic trial (ClinicalTrials.gov identifier). NEDA= no evidence of disease activity (includes new or gadolinium enhancing lesions, relapses, and conformed disability progression). PASAT-3= paced auditory serial addition test 3 seconds. RRMS= relapsing-remitting multiple sclerosis. SPMS= secondary progressive multiple sclerosis. S1P= sphingosine-1-phosphate. PPAR= peroxisome proliferator-activated receptor. T25FW= timed 25-foot walk. 9HPT= 9-hole peg test. mts= months. wks= weeks. yrs=years.
**Studies marked with one asterisk x are phase II trials, despite being listed with other phase III trials.*
***Studies marked with two asterisks are combined Phase I and II trials.*

Drug	Mechanism of Action	Abbreviated Study Name NCT identifier	Duration	Participants	Comparator	Status	Primary Endpoint	Results
PHASE II TRIALS								
ACTH	It acts via corticosteroid-independent melanocortin pathways suppressing CNS proinflammatory cytokines	ACTH in Progressive Forms of MS [NCT01950234]	36 mts	100 PMS (target)	Placebo	Recruiting	T25FW	N/A
Andrographolides (IB-MS)	Medicinal herb with neuroprotective properties that plays a key role in ameliorating innate and adaptive immune reactions. In EAE, andrographolides could suppress T-cell function in the CNS and the maturation of dendritic cells.	Andrographolides Versus Placebo in Patients with Progressive Forms of MS [NCT02273635]	24 mts	43 PMS	Placebo	Completed	Brain atrophy	Negative, but CDP was significantly lower in the active arm.
Dimethyl Fumarate		FUMAPMS [NCT02959658]	48 wks	90 PPMS (target)	Placebo	Recruiting	Neuro filament light chain	N/A
Ibudilast	It is a phosphodiesterase inhibitor with anti-inflammatory properties. It can inhibit nitric oxide synthesis and tumour necrosis factor-α released by activated astrocytes and microglia in the CNS.	SPRINT-MS [NCT01982942]	96 wks	134 PPMS 121 SPMS	Placebo	Completed	Brain atrophy Safety	Positive
Lipoic acid	Antioxidant agent promoting free-radical scavenging, metallic ion chelation and reducing oxidative damage. It inhibits macrophage and microglial activation in EAE.	Lipoic Acid for SPMS [NCT01188811]	2 yrs	54 SPMS	Placebo	Completed	Brain atrophy	Positive
Mesenchymal Cell Therapy	Mesenchymal stem cells, obtained by several sources, have anti-inflammatory, low immunogenicity, and multipotency properties and can differentiate into neurons and glial. Bone marrow and mesenchymal stem cell-derived neural progenitors can stimulate myelin repair processes by endogenous neural precursors, and prevent loss of oligodendrocytes and axons in experimental models of MS.	ACTiMuS [NCT01815632]	2 yrs	80 PMS (target)	Placebo (autologous blood)	Recruiting	GEP	N/A
		MSC-NP [NCT03355365]	27 mts	50 PMS (target)	Placebo	Recruiting	EDSS Plus	N/A
NeuroVax	TCR peptide vaccine able to promote TCR reactive T cells tolerance in MS.	A Study of NeuroVax™, a Novel Therapeutic TCR Peptide Vaccine for SPMS [NCT02149706]	48 wks	150 PMS (target)	Placebo	Not yet recruiting	EDSS	N/A
Oxcarbazepine	It can block sodium channels protecting neurons.	PROXIMUS [NCT02104661]	48 wks	50 early SPMS	Placebo (Patients must be on DMT)	Completed	Neuro filament light chain	Not reported
PHASE III TRIALS								
Biotin (MD1003)	It can promote energy production in demyelinated axons and enhance myelin synthesis in oligodendrocytes.	MS-SPI [NCT02220933]	2 yrs	99 SPMS 55 PPMS	placebo	Completed	EDSS or T25FW (improvement)	Positive
		SPI2 [NCT02936037]	15 mts	600 PMS	Placebo	Active Not recruiting	EDSS or T25FW (improvement)	N/A
Masitinib	It inhibits mast cell activation. Migration and degranulation of mast cells in the CNS release proinflammatory and vasoactive mediators in MS	Masitinib in Patients with PPMS or Relapse-free SPMS** [NCT01433497]	96 wks	450 PMS (target)	Placebo	Recruiting	EDSS	N/A

		(combined phase II/III)						
Simvastatin	Statins can exert anti-inflammatory and protective properties in the CNS. In murine models, statins inhibit MHC class II antigen presentation, induce a shift from a pro-inflammatory Th1 to a Th2 phenotype, downregulate T-cell activation and proliferation, block adhesion molecule expression, inhibit leucocyte migration through the BBB, and improve cerebrovascular haemodynamics.	MS-STAT* [NCT00647348]	24 mts	140 SPMS	Placebo	Completed	Brain atrophy	Positive
		MS-STAT2 [NCT03387670]	36 mts	1180 SPMS (target)	Placebo	Recruiting	EDSS	N/A
Siponimod	Selective modulator of S1P1 and S1P5 receptors, which induce lymphocyte sequestration in lymph nodes avoiding lymphocytes to cross the BBB. Siponimod can cross the BBB, reduce CNS inflammation and promote mechanisms of repair via modulation of S1P1 on astrocytes and S1P5 on oligodendrocytes.	EXPAND [NCT01665144]	3 yrs	1652 SPMS	Placebo	Active Not recruiting (extension ongoing)	EDSS	Positive

Table 2 Clinical trials in progressive multiple sclerosis showing promising results or currently ongoing (source clinicaltrials.gov, last accessed October 22, 2018).
Only double-blind randomised clinical trials with an efficacy primary endpoint have been included. ACTH= adrenocorticotropic hormone. BBB= blood–brain barrier. BDNF= brain-derived neurotrophic factor. CNS= central nervous system. DMT= disease-modifying therapy. EDSS= Expanded Disability Status Scale. GEP= global evoked potential. IFNβ= interferon beta. MSFC= multiple sclerosis functional composite. MTR= magnetic transfer ratio. N/A= not applicable. RRMS= relapsing-remitting multiple sclerosis. SPMS= secondary progressive multiple sclerosis. S1P= sphingosine-1-phosphate. NCT= number clinic trial (ClinicalTrials.gov identifier). TCR= T-cell receptor. T25FW= timed 25-foot walk. mts= months. wks= weeks. yrs=years.
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