Catania, Piazza Duomo

Sclerosi Multipla

Innovazione terapeutica

Congresso Regionale SIN Sicilia
Catania, 15 Febbraio 2019

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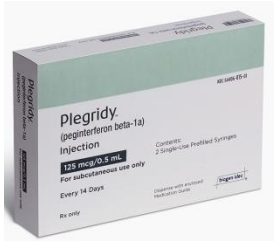
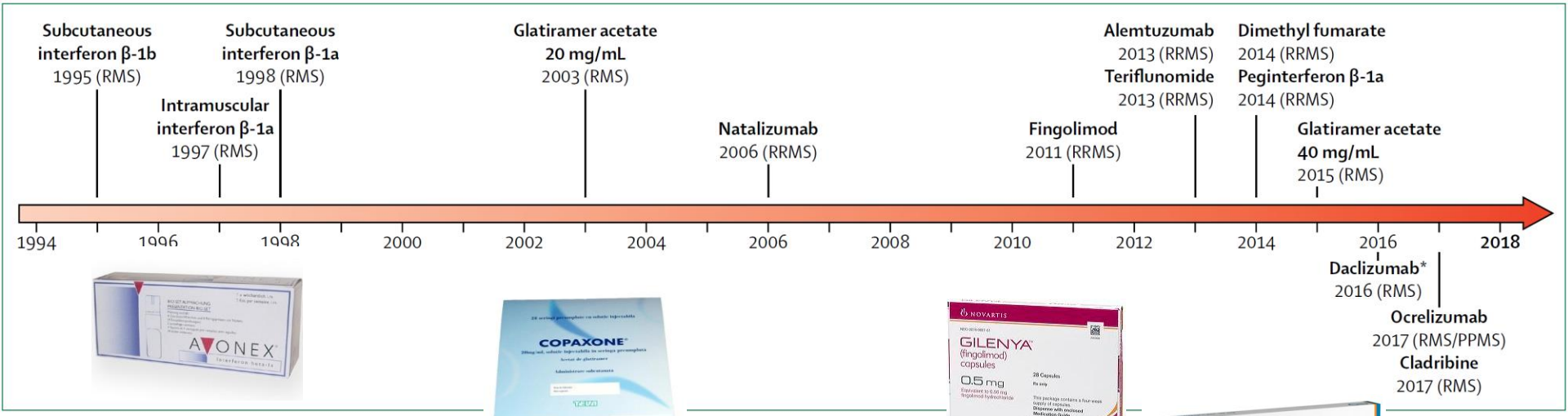
Direttore UOC Neurologia
PO S. Elia, Caltanissetta





Thompson AJ et al, *Lancet* 2018;391:1622-1636

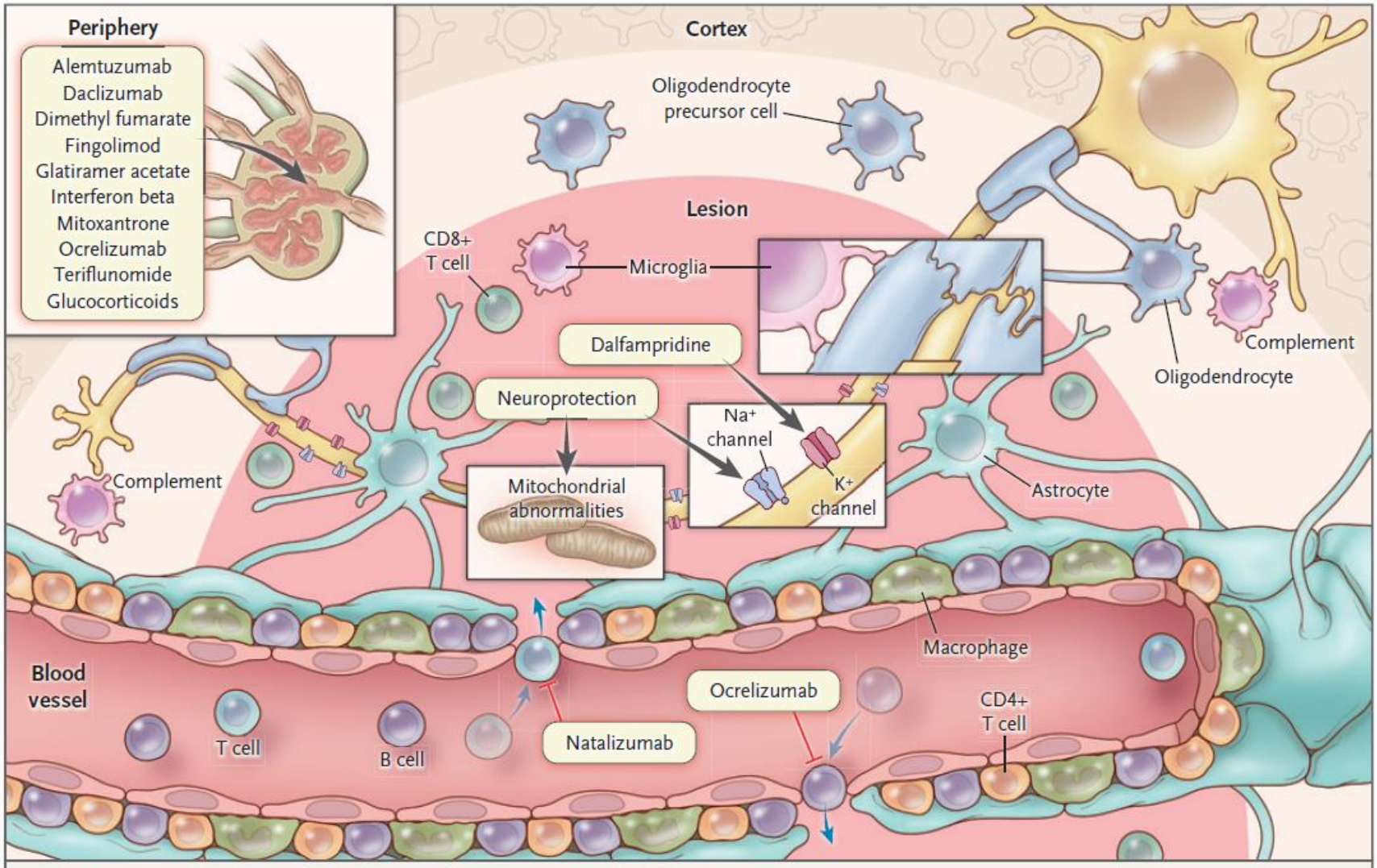
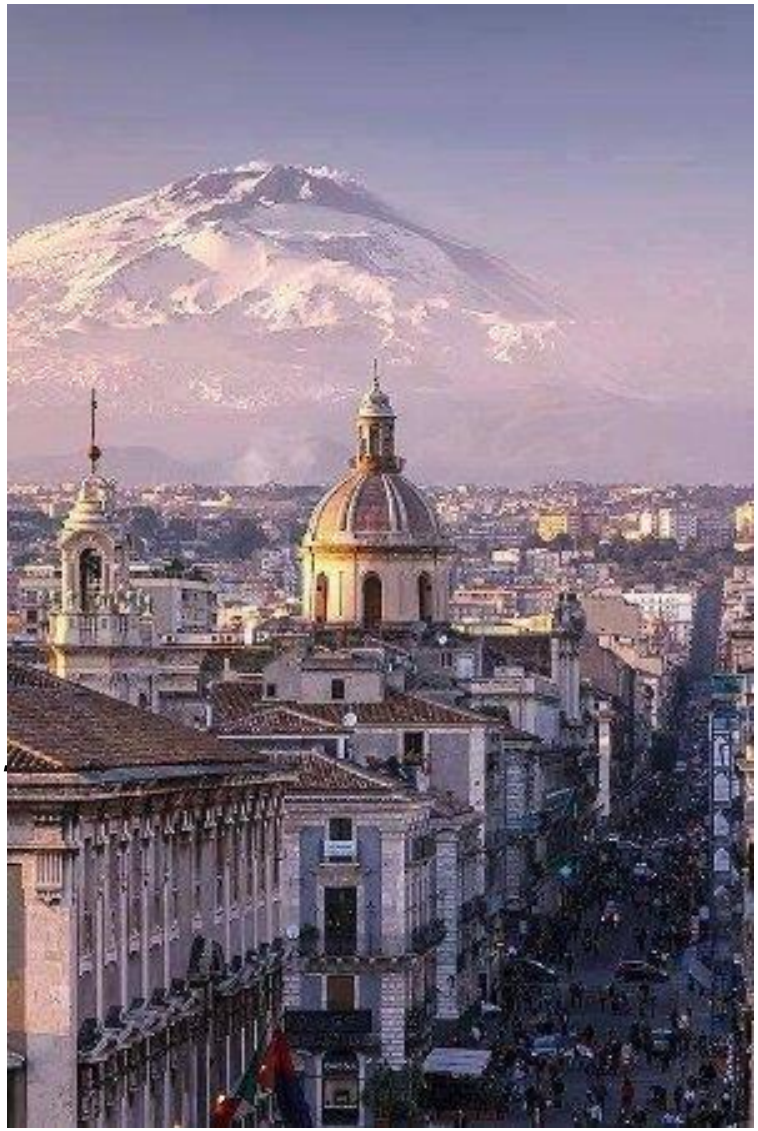


Figure 4. Cells, Molecules, and Therapies.

Shown is a simplified schematic depiction of major cell types within white-matter multiple sclerosis lesions, along with several current and promising therapeutic targets in the central nervous system and in the periphery.

Reich DS et al, *N Engl J Med* 2018;378:169-80


Catania - Via Etnea e l'Etna



Ongoing clinical trials

- Siponimod
- Amiselimod
- Ozanimod

Sphingosine 1-phosphate receptor (S1PR) modulators

- Ibudilast
- Simvastatin
- Phenytoin

Neuroprotective strategies

- Biotin
- Clemastine

Remyelinating therapy

- Minocycline
- Masitinib

Other mechanisms

Sphingosine 1-phosphate receptor (S1PR) modulators

Receptor	Drug	Associated cell types	Function
S1PR1	Fingolimod Siponimod Ozanimod Ceralifimod GSK2018682 Ponesimod MT-1303	Lymphocytes Neurons Endothelial cells AV node and Conduction system Smooth muscle	Egress from lymph nodes Neuron migration and function Permeability barrier Heart rate slowing Permeability barrier
S1PR2	✕	CNS Endothelial cells Smooth muscle	Hearing and balance Permeability barrier Vascular tone
S1PR3	Fingolimod	Neurons AV node and Conduction system Endothelial cells Smooth muscle	Neuron migration and function Slowed heart conduction Permeability barrier
S1PR4	Fingolimod	Lymphocytes	Lymphoid tissue expression Dendritic and TH17 cell modulation
S1PR5	Fingolimod Siponimod Ozanimod Ceralifimod GSK2018682	CNS Natural killer cells	Oligodendrocyte function Natural killer cell migration

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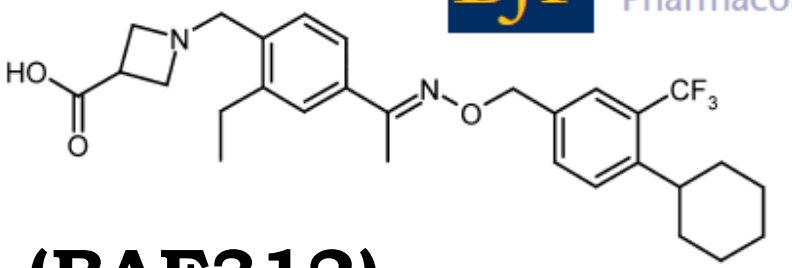
Chaudhry BZ et al, *Neurotherapeutics* 2017;14:859-873

The selective sphingosine 1-phosphate receptor modulator BAF312 redirects lymphocyte distribution and has species-specific effects on heart rate

BJP British Journal of Pharmacology



Siponimod (BAF312)

❖Selectively modulates sphingosine-1-phosphate (S1P) receptors S1P1 and S1P5.

❖Reduces egress of lymphocytes from lymphoid tissues and prevents recirculation of peripheral lymphocytes to the CNS.

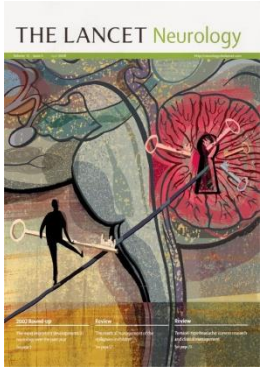
❖Caused preferential decreases in CD4+ T cells, T naïve, T central memory and B cells within 4–6 h.

❖Cell counts returned to normal ranges within a week after stopping treatment, in line with the elimination half-life of BAF312.

❖Induced rapid, transient (at 2 h after the first dose) bradycardia in humans through the activation of GIRK channels.

Gergely P et al, *Br J Pharmacol* 2012;167:1035-47

Siponimod for patients with relapsing-remitting multiple sclerosis (BOLD): an adaptive, dose-ranging, randomised, phase 2 study



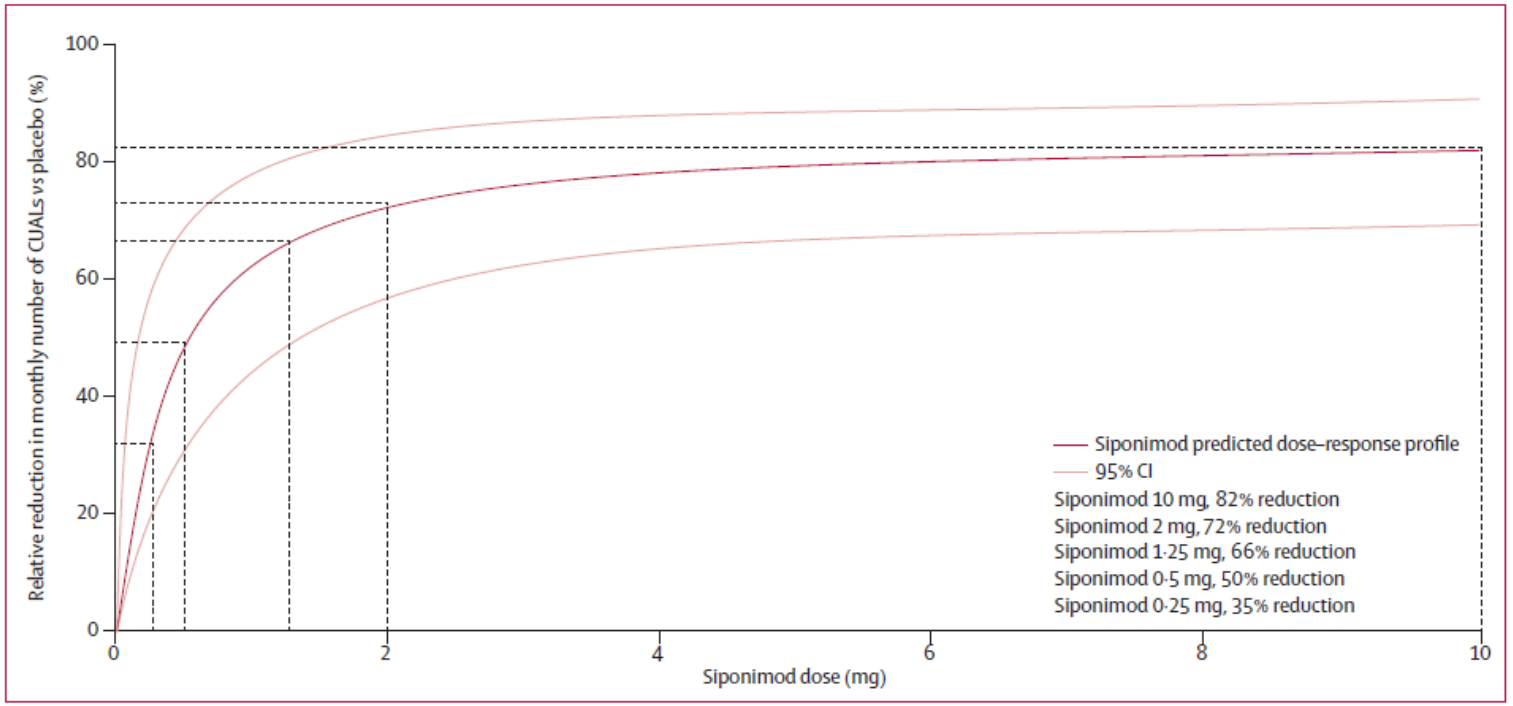
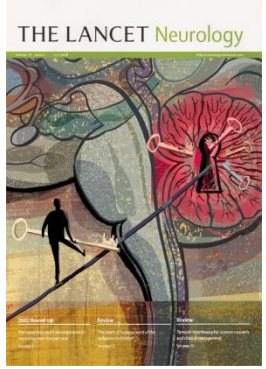
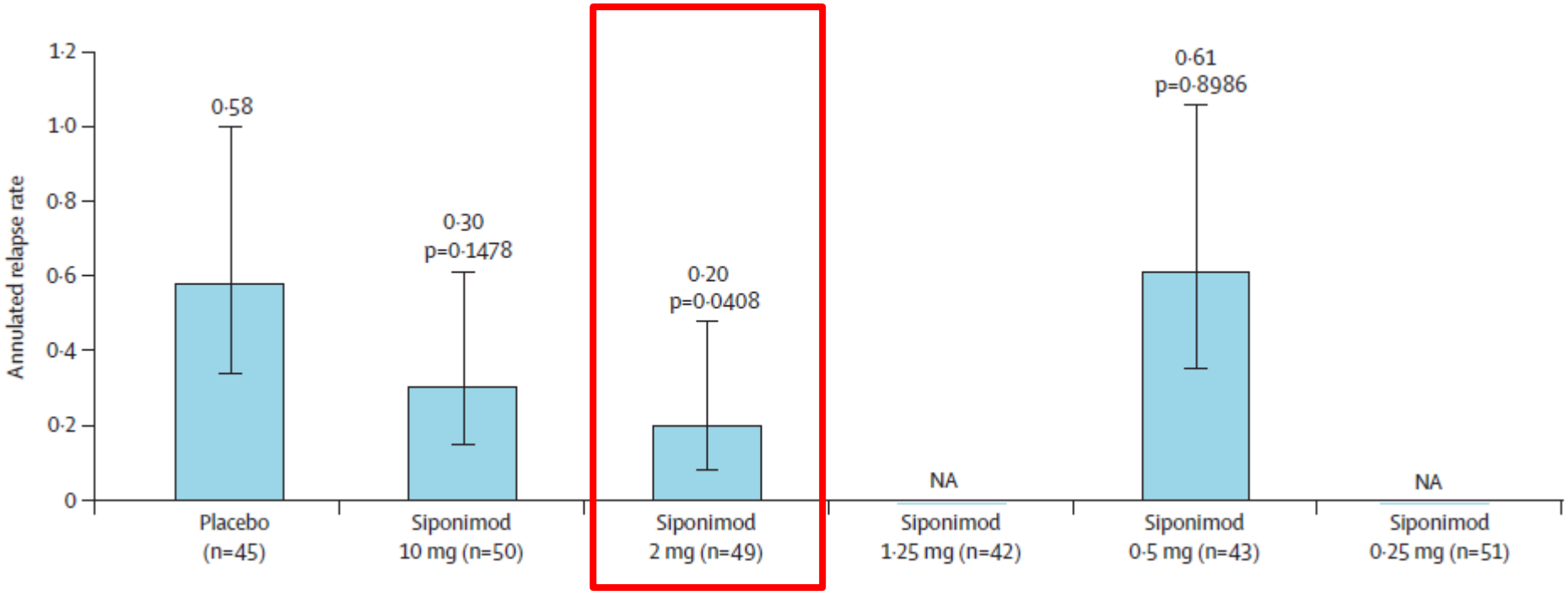


***Figure 3*: Bayesian longitudinal dose-response curve at month 3 and relative reductions versus placebo in number of CUALs (primary outcome)**
We assessed the primary endpoint with MCP-mod methods,[9] adapted for lesion count data; for this adapted method, we used a predefined negative binomial model to describe CUAL count over time and an E_{max} model was selected to fit the dose-response profile best over 3 months. A Bayesian model[8] was also chosen to fit the CUAL count data observed at month 3. The resulting siponimod dose-response curve was summarised by a plot of the posterior median estimate and associated 95% CIs and by the dose achieving a 50% relative reduction in CUAL count versus placebo. CUAL=combined unique active lesion. MCP-mod=multiple comparison procedure with modelling techniques.

Selmaj K et al, *Lancet Neurol* 2013 ;12:756-67

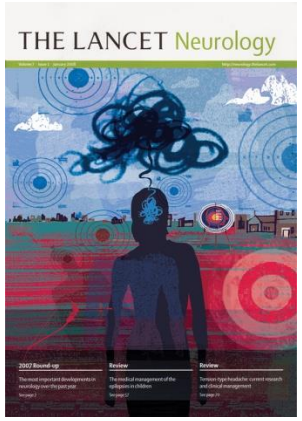
Siponimod for patients with relapsing-remitting multiple sclerosis (BOLD): an adaptive, dose-ranging, randomised, phase 2 study



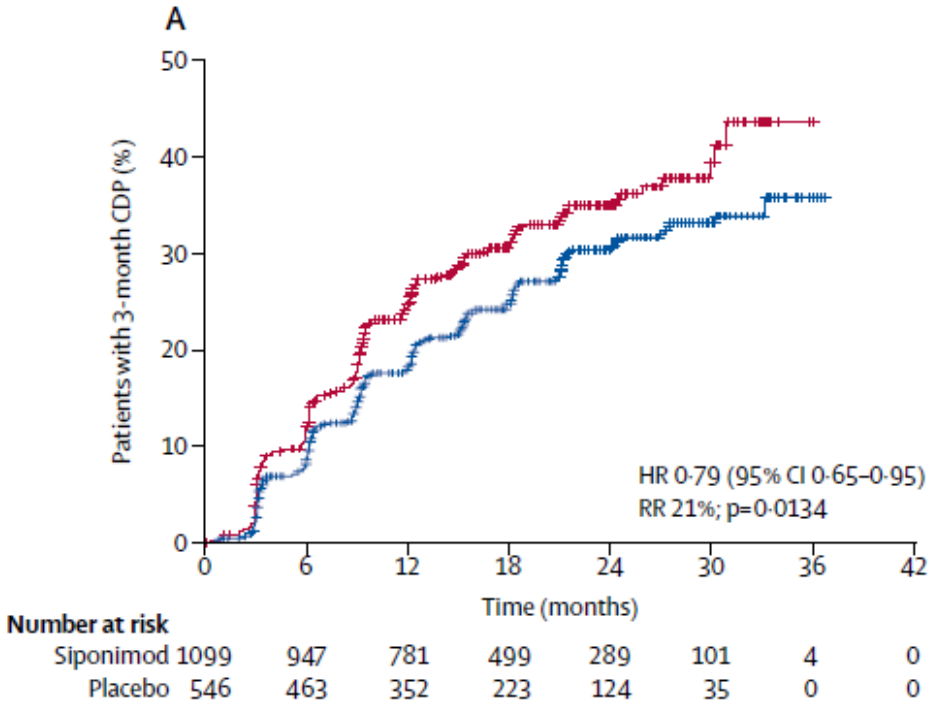


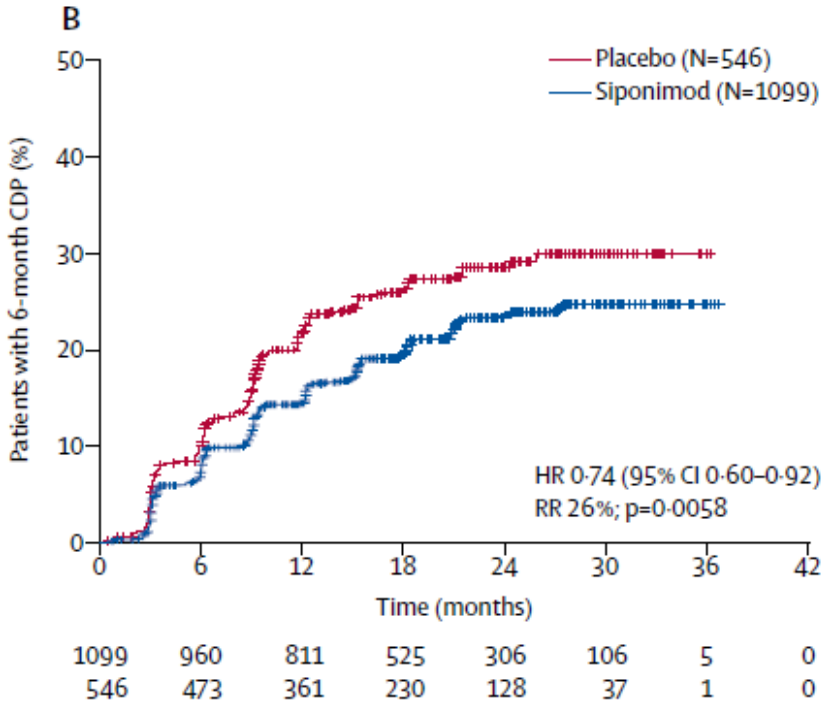
Significant reduction of ARR at dose of siponimod 2 mg vs placebo

Selmaj K et al, *Lancet Neurol* 2013 ;12:756-67



Siponimod versus placebo in secondary progressive multiple sclerosis (EXPAND): a double-blind, randomised, phase 3 study



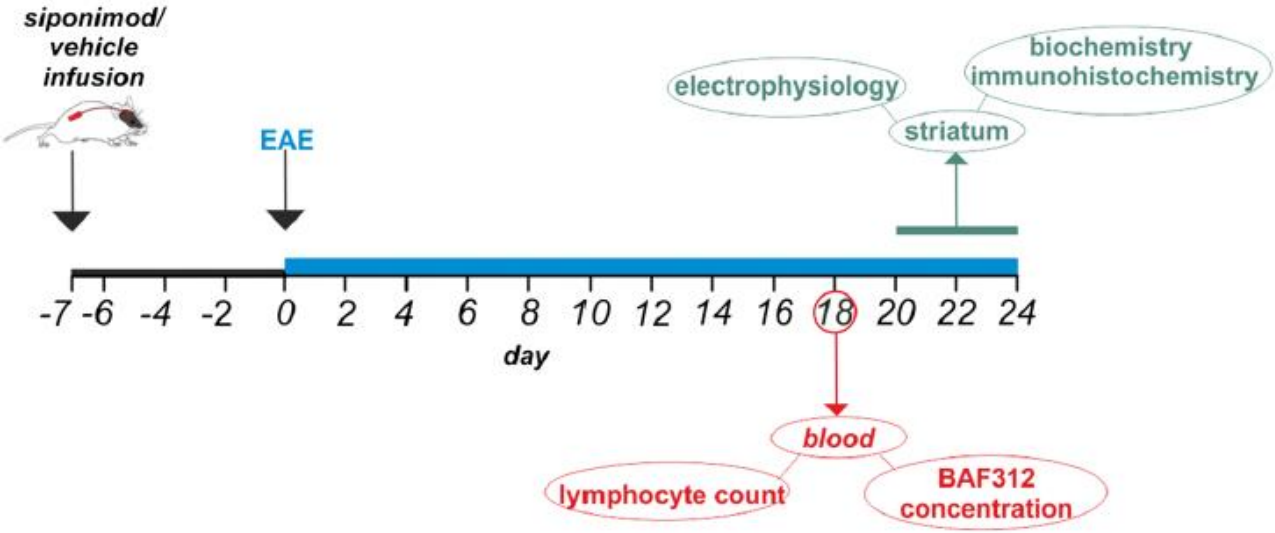


Siponimod significantly reduced 3-month CDP (confirmed disability progression) compared with placebo in SMSP patients.

Kappos L et al, *Lancet* 2018;391:1263-1273

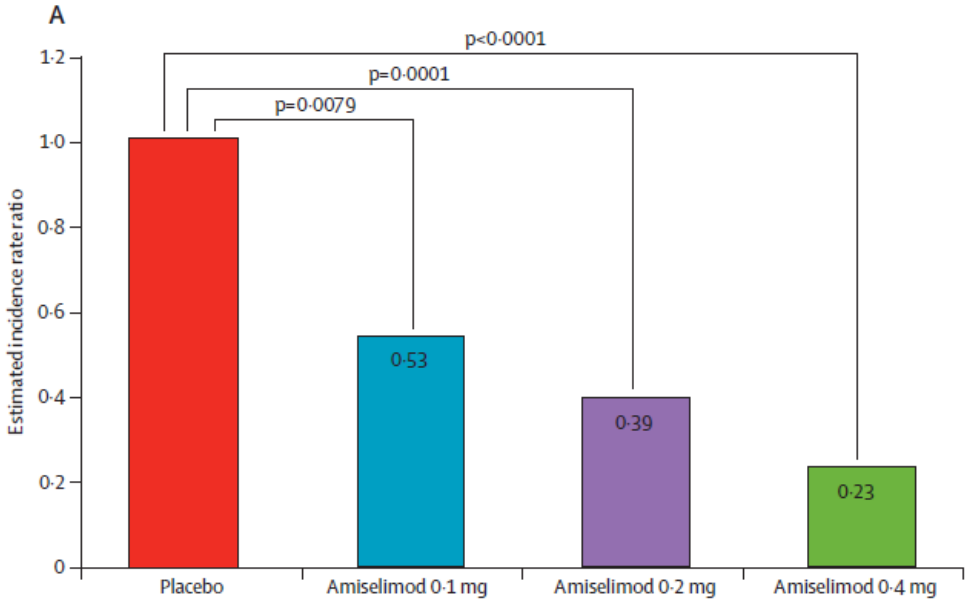
Siponimod (BAF312) prevents synaptic neurodegeneration in experimental multiple sclerosis

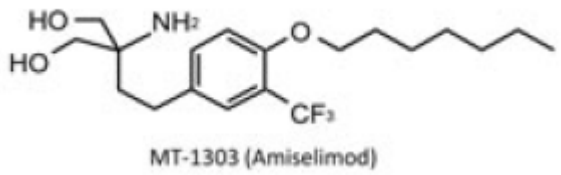
Results: Siponimod administration (0.45 μg/day) induced a significant beneficial effect on EAE clinical scores with minimal effect on peripheral lymphocyte counts. Siponimod rescued defective GABAergic transmission in the striatum of EAE, without correcting the EAE-induced alterations of glutamatergic transmission. We observed a significant attenuation of astrogliosis and microgliosis together with reduced lymphocyte infiltration in the striatum of EAE mice treated with siponimod. Interestingly, siponimod reduced the release of IL-6 and RANTES from activated microglial cells in vitro, which might explain the reduced lymphocyte infiltration. Furthermore, the loss of parvalbumin-positive (PV+) GABAergic interneurons typical of EAE brains was rescued by siponimod treatment, providing a plausible explanation of the selective effects of this drug on inhibitory synaptic transmission.



Gentile A et al. *J Neuroinflammation* 2016;13:207

Safety and efficacy of amiselimod in relapsing multiple sclerosis (MOMENTUM): a randomised, double-blind, placebo-controlled phase 2 trial





MT-1303 (Amiselimod)

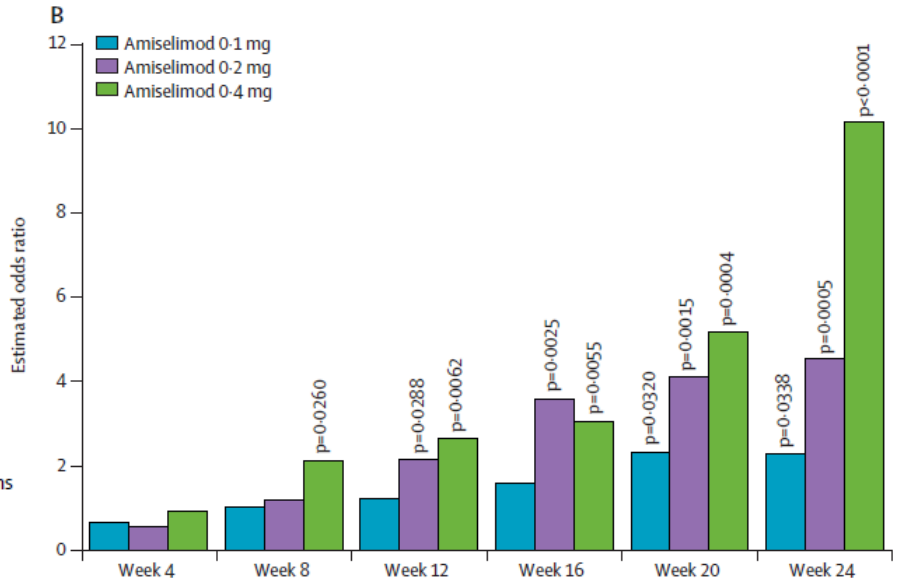
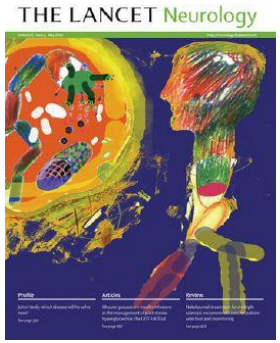


Figure 2: **Effect of amiselimod on gadolinium-enhanced T1-weighted lesions**
(A) Estimated incidence rate ratio *vs* placebo in the total number of gadolinium-enhanced T1-weighted lesions from weeks 8 to 24. (B) Estimated odds ratio *vs* placebo for being free of gadolinium-enhanced T1-weighted lesions by visit. p values are based on a binary generalised estimating equations model with an indicator of lesion free at each post-dose visit as the response variable. The independent variables are treatment, visit, treatment-by-visit interaction, and pooled centre as fixed effects.

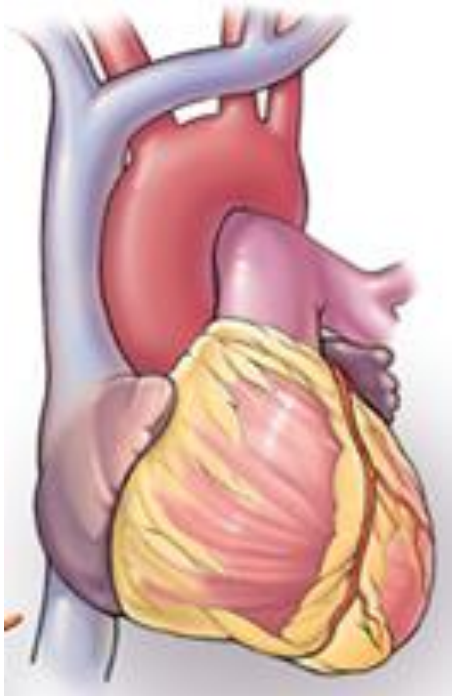
Amiselimod 0·2 mg and 0·4 mg significantly reduced the total number of gadolinium-enhanced T1-weighted lesion from weeks 8 to 24 (primary endpoint).

Kappos L et al. *Lancet Neurol.* 2016;15:1148-59



Safety and efficacy of amiselimod in relapsing multiple sclerosis (MOMENTUM): a randomised, double-blind, placebo-controlled phase 2 trial

❖In Holter ECG analysis, no clinically relevant bradycardia, sinus pause (≥3 s), or atrioventricular blocks (ie, Mobitz type 2 second-degree atrioventricular block, 2:1 atrioventricular block, high grade atrioventricular block, or complete heart block) occurred in any amiselimod group.



❖Unlike other S1P receptor modulators, there were no clinically significant effects on cardiac rhythm in any of the amiselimod doses tested, without the need of a dose titration regimen.

Kappos L et al. *Lancet Neurol.* 2016;15:1148-59

Safety and efficacy of the selective sphingosine 1-phosphate receptor modulator ozanimod in relapsing multiple sclerosis (RADIANCE): a randomised, placebo-controlled, phase 2 trial

- Ozanimod is a novel, oral, selective, small-molecule S1PR1 and S1PR5 modulator
- Does not need phosphorylation for activation.
- Short half-life (19 h), allowing for once-daily dosing.
- Dose dependent decrease in circulating lymphocyte counts, but with rapid lymphocyte recovery after discontinuation.
- It crosses the blood–brain barrier and has a low peak plasma concentration because of its high volume of distribution and delayed absorption, leading to low systemic exposure that reduces the first-dose effects on heart rate.
- A therapeutic dose-titration regimen further mitigates potential first-dose cardiac effects

Cohen JA et al, *Lancet Neurol*. 2016;15:373-81

THE LANCET Neurology

Safety and efficacy of the selective sphingosine 1-phosphate receptor modulator ozanimod in relapsing multiple sclerosis (RADIANCE): a randomised, placebo-controlled, phase 2 trial

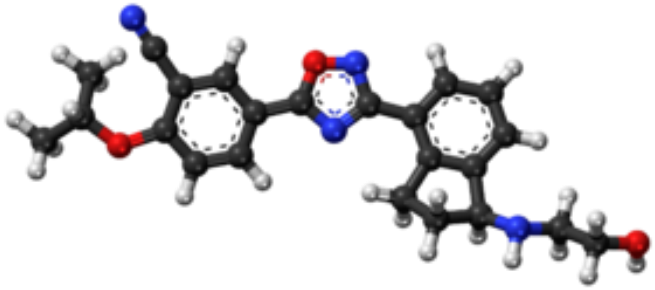
	Placebo (n=88)	Ozanimod 0·5 mg (n=87)	Ozanimod 1 mg (n=83)
MRI outcomes			
Mean (SD) cumulative number of gadolinium-enhancing lesions, weeks 12–24 (primary endpoint)	11·1 (29·9)	1·5 (3·7)	1·5 (3·4)
Odds ratio (95% CI) *vs* placebo	..	0·16 (0·08–0·30); p<0·0001	0·11 (0·06–0·21); p<0·0001
Mean (SD) number of gadolinium-enhancing lesions, week 24 (secondary endpoint)	3·2 (9·8)	0·3 (0·9)	0·2 (0·6)
Odds ratio (95% CI) *vs* placebo	..	0·16 (0·07–0·34); p<0·0001	0·06 (0·02–0·15); p<0·0001
Mean (SD) cumulative number of new or enlarging T2 lesions, weeks 12–24 (secondary endpoint)	9·0 (20·9)	1·4 (3·2)	0·8 (1·9)
Odds ratio (95% CI) *vs* placebo	..	0·17 (0·10–0·30); p<0·0001	0·08 (0·04–0·14); p<0·0001
Clinical outcome			
Mean (95% CI) annualised relapse rate (secondary endpoint)*	0·5 (0·2–1·2)	0·35 (0·2–0·8)	0·24 (0·1–0·6)
Odds ratio (95% CI) *vs* placebo	..	0·69 (0·36–1·34); p=0·2714	0·47 (0·22–1·01); p=0·0531

No adjustments to the point estimates and CI were made. *Odds ratio and p value from a Poisson regression model adjusted for region, number of relapses in the previous 24 months, and presence of gadolinium-enhancing lesions at baseline.

Table 2: **MRI and clinical outcomes (intention-to-treat population)**

Cohen JA et al, *Lancet Neurol.* 2016;15:373-81

Ozanimod demonstrates efficacy and safety in a phase 3 trial of relapsing multiple sclerosis (SUNBEAM)



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EUROPEAN COMMITTEE FOR TREATMENT AND RESEARCH IN MULTIPLE SCLEROSIS

Methods:

❖This was a multicenter, randomized, double-blind, double-dummy, parallel-group, active treatment-controlled, study of daily oral ozanimod 0.5 or 1 mg vs. weekly IFN β-1a, 30 μg IM injection.

❖The primary endpoint was annualized relapse rate (ARR) for each ozanimod dose vs IFN β-1a.

❖Key secondary endpoints included magnetic resonance imaging (MRI) assessments to measure new and enlarging T2 lesions from baseline to month 12 and T1, gadolinium enhancing lesions (GdE) at month 12.

ECTRIMS Online Library. Comi G. Oct 27, 2017; 202595

Ozanimod demonstrates efficacy and safety in a phase 3 trial of relapsing multiple sclerosis (SUNBEAM)

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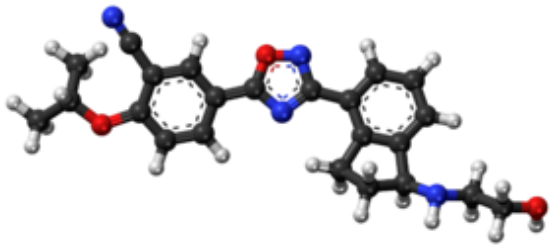


Results: A total of 1,346 RMS patients were enrolled in 20 countries with baseline characteristics similar across treatment groups. In the SUNBEAM trial, a significant reduction in ARR was demonstrated for ozanimod 1 mg (ARR = 0.18; $p < 0.0001$) and for ozanimod 0.5 mg (ARR = 0.24; $p = 0.0013$) compared with IFβ-la (Avonex) (ARR = 0.35) Ozanimod demonstrated a significant reduction in new or enlarging T2 lesions over one year for 1 mg (48%; $p<0.0001$) and 0.5 mg (25%; $p = 0.0032$) compared with IFβ-1a (Avonex). A significant reduction in gadolinium enhanced MRI lesions at one year was also demonstrated for ozanimod 1 mg (63%; $p < 0.0001$) and ozanimod 0.5 mg (34%; $p = 0.0182$) compared with IFβ-1a (Avonex).

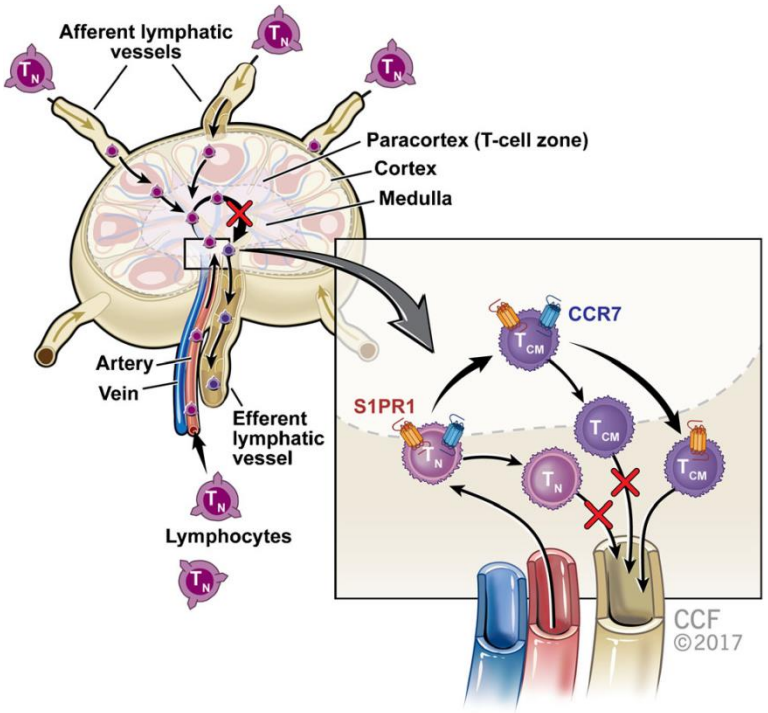
Conclusion: In this Phase 3 study, both doses of ozanimod demonstrated superiority to IFN β-1a on relapse and MRI endpoints. This, coupled with the safety and tolerability results, demonstrates a favourable benefit risk profile for ozanimod in RRMS.

ECTRIMS Online Library. Comi G. Oct 27, 2017; 202595

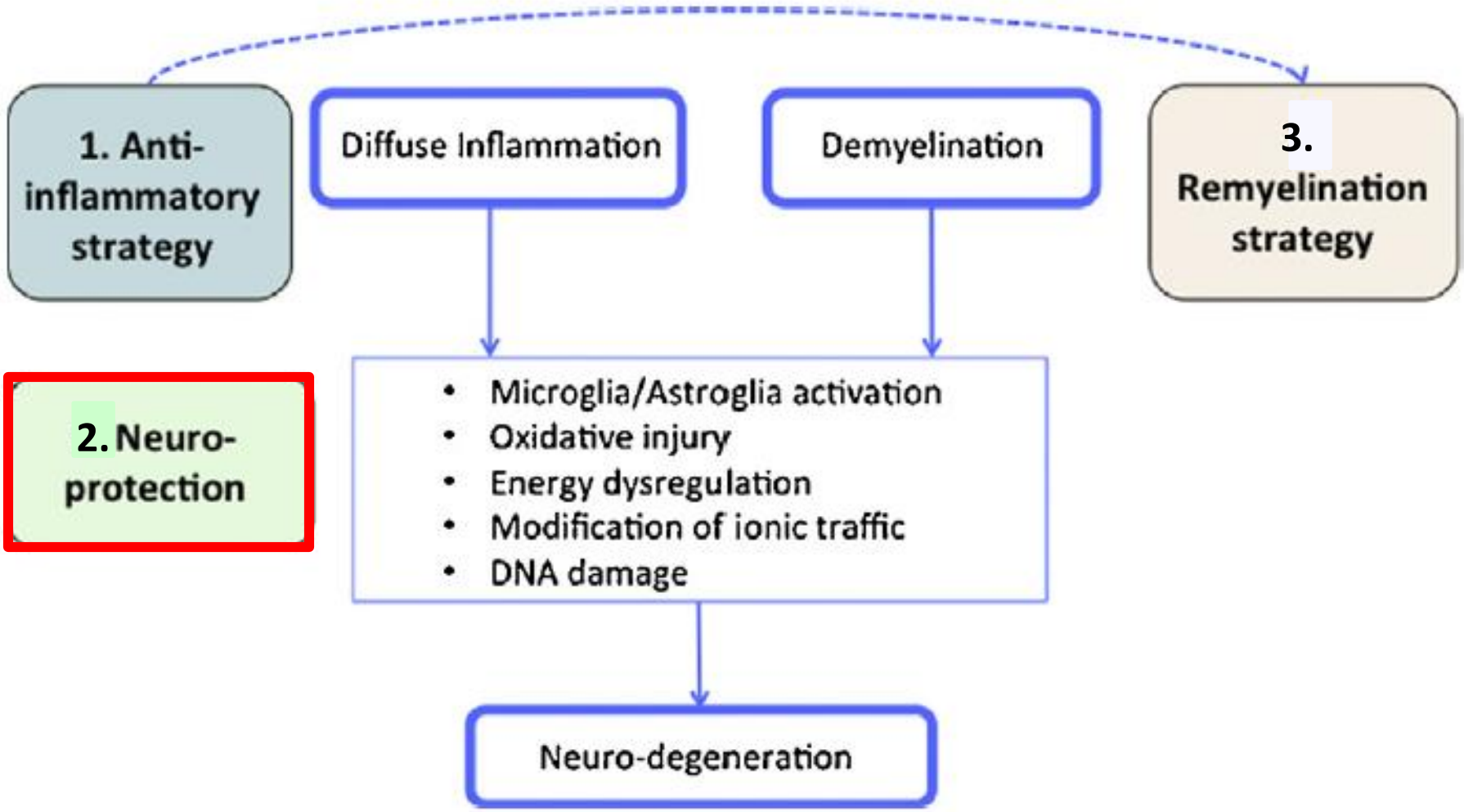
Second-generation S1PR modulators

❖The advent of second-generation S1PR modulators with greater specificity for S1PR1 will likely expand the population of patients with MS who can benefit from this class of medication.

❖In addition to a lower risk for treatment complications such as bradycardia, the shorter half-lives of the second generation medications will increase safety, especially if complications such as PML arise.



Chaudhry BZ et al, *Neurotherapeutics* 2017;14:859-873



Maillart E. *Rev Neurol* .2018;174:441-448

Phase 2 Trial of Ibudilast in Progressive Multiple Sclerosis

❖Ibudilast inhibits several cyclic nucleotide phosphodiesterases, macrophage migration inhibitory factor, and toll-like receptor4 and can cross the blood–brain barrier.

❖Phase 2 randomized trial of oral ibudilast (≤100 mg daily) or placebo for 96 weeks.

❖Patients with primary or secondary progressive multiple sclerosis (129 received ibudilast, 126 received placebo).

❖The primary efficacy end point was the rate of brain atrophy, as measured by the brain parenchymal fraction.

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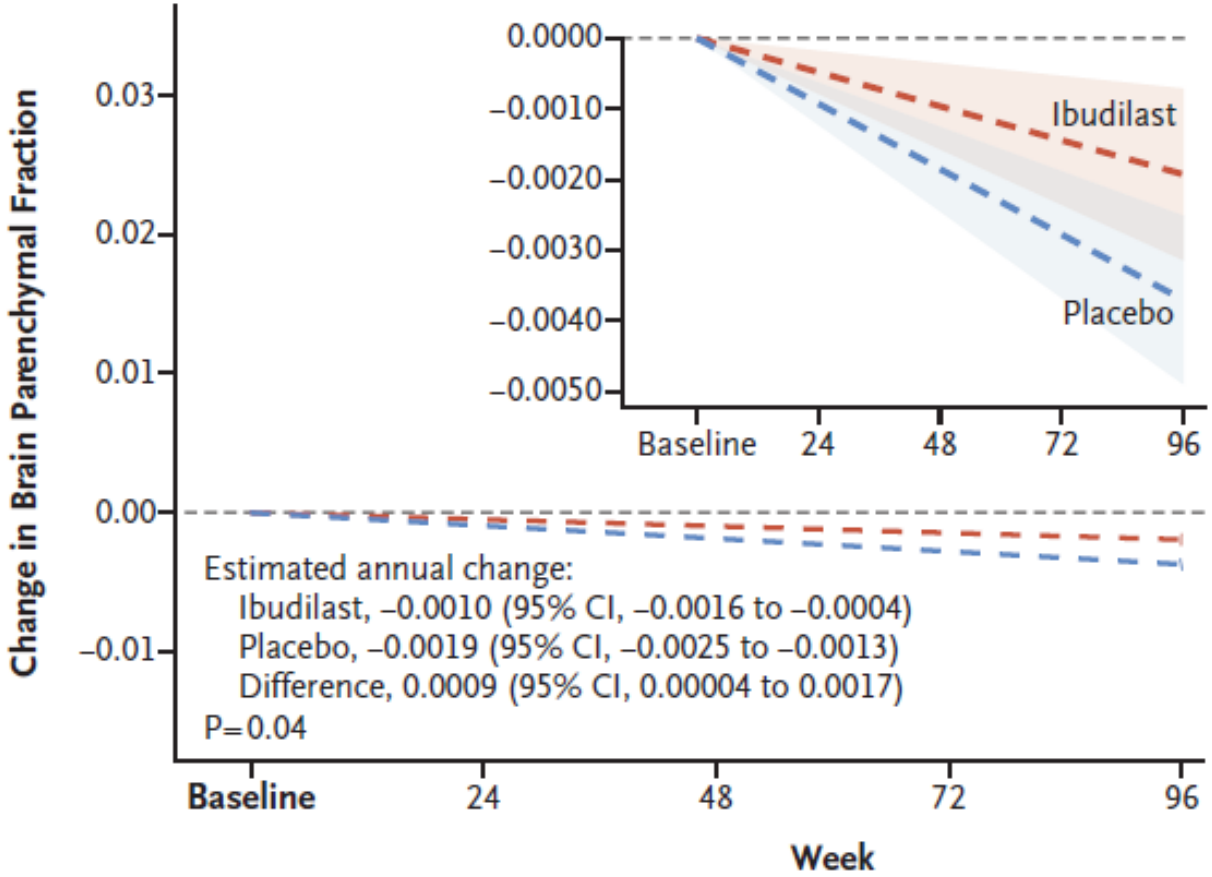
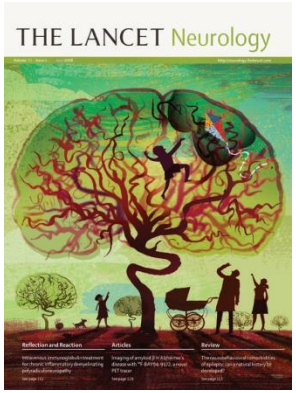
Fox RJ et al, *N Engl J Med.* 2018;379:846-855

Phase 2 Trial of Ibudilast in Progressive Multiple Sclerosis



Approximately 2.5 ml less brain-tissue loss with ibudilast than with placebo over a period of 96 weeks, and a relative difference of 48%.

Fox RJ et al, *N Engl J Med.* 2018;379:846-855

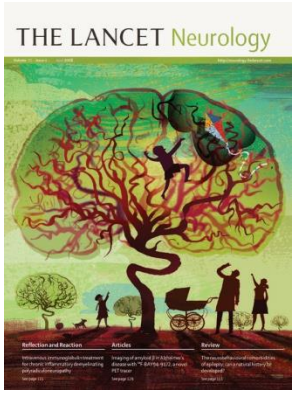


Effect of high-dose simvastatin on brain atrophy and disability in secondary progressive multiple sclerosis (MS-STAT): a randomised, placebo-controlled, phase 2 trial

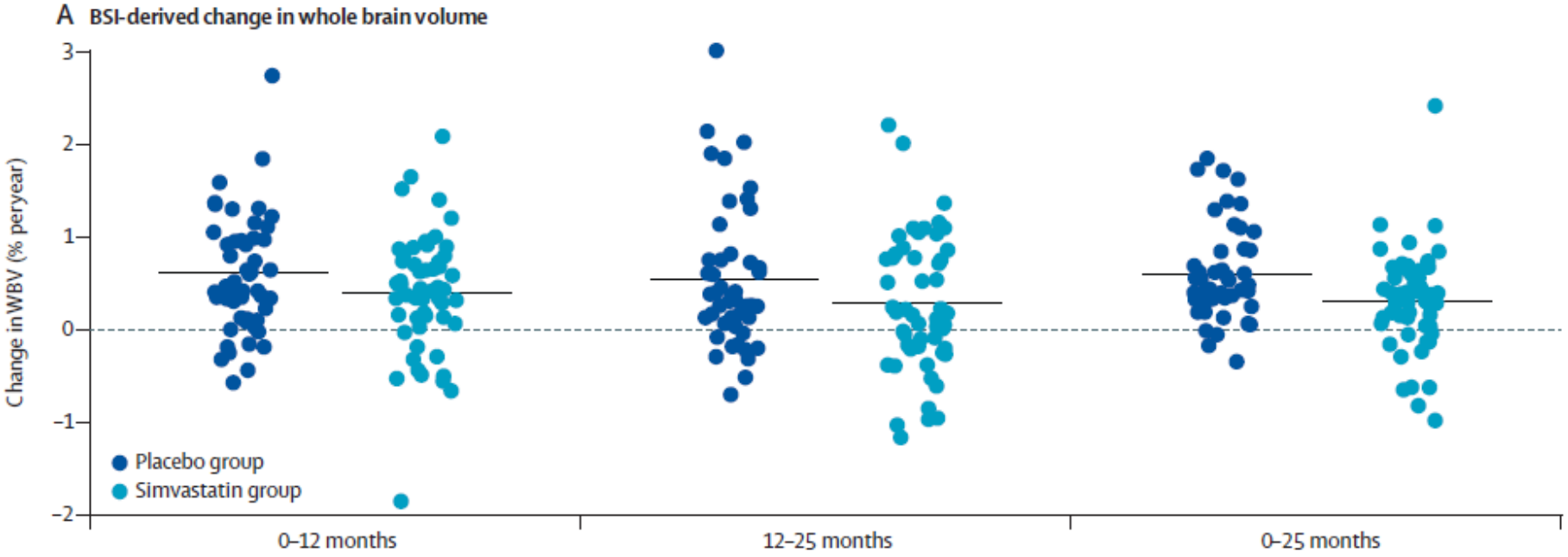
	Placebo (n=70)	Simvastatin (n=70)	Difference in means*	95% CI for difference
Change in whole-brain volume (% per year)*†				
Mean (SD) rate	0·584 (0·498)	0·288 (0·521)	−0·254‡	−0·422 to −0·087
Number (%) assessed	64 (91%)	66 (94%)	..	..
Number of BBSI measures	165	175	..	..

Compared with placebo, simvastatin 80 mg per day reduced the annualised rate of whole-brain atrophy by 43%.

Chataway J et al, *Lancet*. 2014;383:2213-21



Effect of high-dose simvastatin on brain atrophy and disability in secondary progressive multiple sclerosis (MS-STAT): a randomised, placebo-controlled, phase 2 trial



Between 0 and 25 months more than three quarters of patients in the simvastatin group had a lower atrophy rate than the mean rate in the placebo group.

Chataway J et al, *Lancet*. 2014;383:2213-21

Phenytoin for neuroprotection in patients with acute optic neuritis: a randomised, placebo-controlled, phase 2 trial

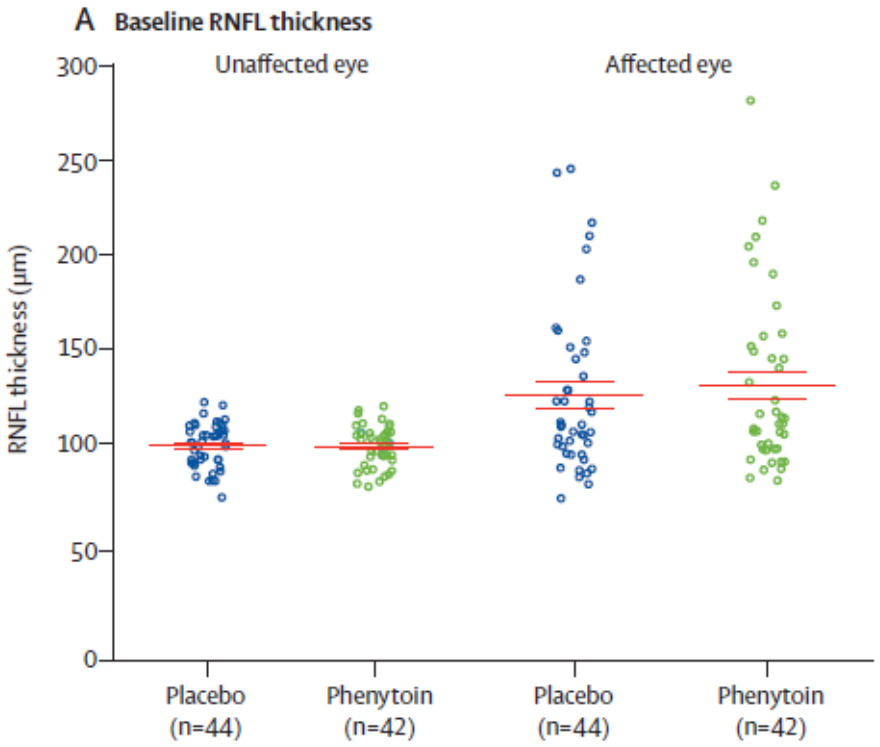
❖In acute relapses, evidence is growing of a cascade arising from neuronal energy failure, leading in turn to reduced activity of the membrane sodium potassium ATPase, accumulation of sodium ions entering mainly via NaV channels, reverse operation of the membrane sodium-calcium exchanger, and finally toxic accumulation of calcium ions. NaV channels are also likely to play an important role in microglia activation and subsequent immune attack.

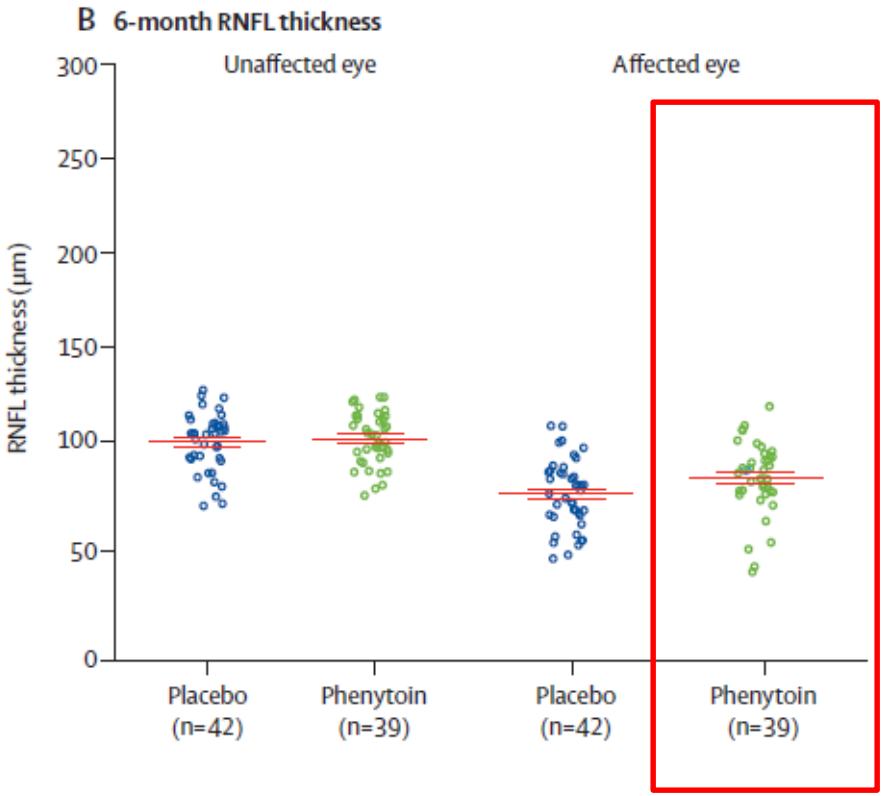
❖ Voltage-gated sodium-channel inhibitors are neuroprotective in several preclinical models of neuroinfl ammation.

❖Phenytoin, a selective sodium-channel inhibitor, is neuroprotective at therapeutic concentrations in experimental models.

Raftopoulos R et al, *Lancet Neurol*. 2016;15:259-69

Phenytoin for neuroprotection in patients with acute optic neuritis: a randomised, placebo-controlled, phase 2 trial





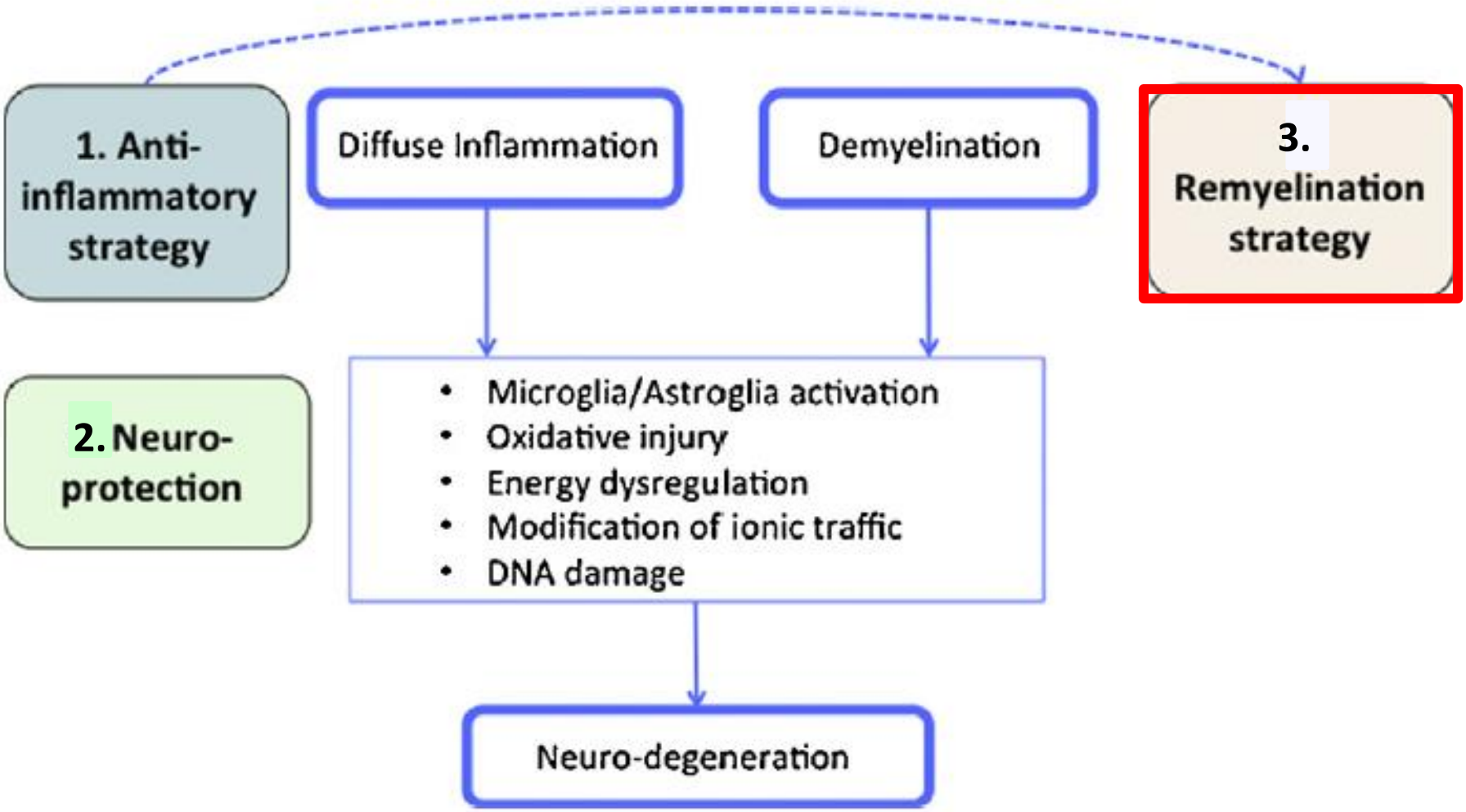
Raftopoulos R et al, *Lancet Neurol.* 2016;15:259-69

Phenytoin for neuroprotection in patients with acute optic neuritis: a randomised, placebo-controlled, phase 2 trial

	Baseline				6 months					
	Phenytoin		Placebo		Phenytoin		Placebo		Adjusted* 6-month difference† (95% CI)	p value
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)		
RNFL thickness, µm	42	130·62 (46·4)	44	125·20 (43·4)	39	81·46 (16·27)	42	74·29 (15·14)	7·15 (1·08 to 13·22)	0·021
Macular volume, mm³	42	8·71 (0·46)	44	8·63 (0·43)	39	8·25 (0·45)	41	8·07 (0·42)	0·20 (0·06 to 0·34)	0·005
Optic nerve cross-sectional area, mm²	34	7·60 (1·55)	39	7·48 (1·43)	31	4·58 (0·88)	34	4·48 (1·01)	0·40 (−0·02 to 0·83)	0·061
Lesion length, mm	39	17·2 (8·1)	42	18·0 (7·1)	34	15·15 (7·62)	36	17·17 (10·11)	−2·45 (−6·97 to 2·08)	0·285
VEP latency, ms‡	39	167·9 (35·2)	43	167·6 (35·8)	35	133·0 (24·8)	40	127·4 (19·3)	5·71 (−4·56 to 15·99)	0·271
VEP amplitude, µV ‡	39	2·7 (3·8)	43	3·0 (3·8)	35	7·1 (4·6)	40	7·3 (4·6)	−0·18 (−1·83 to 1·46)	0·827
LogMAR visual acuity	42	1·08 (0·56)	44	1·04 (0·62)	39	0·09 (0·40)	42	0·04 (0·18)	0·02 (−0·11 to 0·16)	0·728
Low-contrast letter score (1·25%)	42	0·07 (0·46)	44	0·45 (3·02)	39	13·38 (12·14)	42	12·33 (12·13)	1·19 (−4·16 to 6·53)	0·660
Low-contrast letter score (2·5%)	42	0·21 (1·24)	44	0·77 (3·83)	39	19·69 (13·80)	42	17·55 (14·19)	2·07 (−4·10 to 8·25)	0·506
FM 100-hue total error score	42	1066 (764·6)	43	1139 (775·5)	39	181·28 (223·79)	42	195·24 (212·61)	−18·46 (−116·44 to 79·51)	0·708

Use of phenytoin was associated with a significant reduction in the loss of RNFL thickness and macular volume after acute optic neuritis, probably through a protective effect on ganglion cells (which make up about 34% of macular volume) and their axons in the RNFL and the optic nerve via partial inhibition of voltage-gated sodium channels.

Raftopoulos R et al, *Lancet Neurol*. 2016;15:259-69

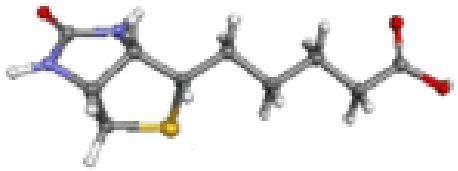


Maillart E. *Rev Neurol* .2018;174:441-448

MD1003 (high-dose biotin) for the treatment of progressive multiple sclerosis: A randomised, double-blind, placebo-controlled study

❖MD1003 is an oral formulation of high-dose pharmaceutical- grade biotin (10,000 times the recommended daily intake) that demonstrated promising efficacy in patients with not-active progressive MS in a pilot open-label study

❖Biotin is a coenzyme for many essential carboxylases and, in high doses, is hypothesised to enhance cellular energy production with resultant improved axonal function, decreased neurodegeneration, and enhanced remyelination.



Tourbah A et al, *Mult Scler*. 2016;22:1719-1731

MD1003 (high-dose biotin) for the treatment of progressive multiple sclerosis: A randomised, double-blind, placebo-controlled study

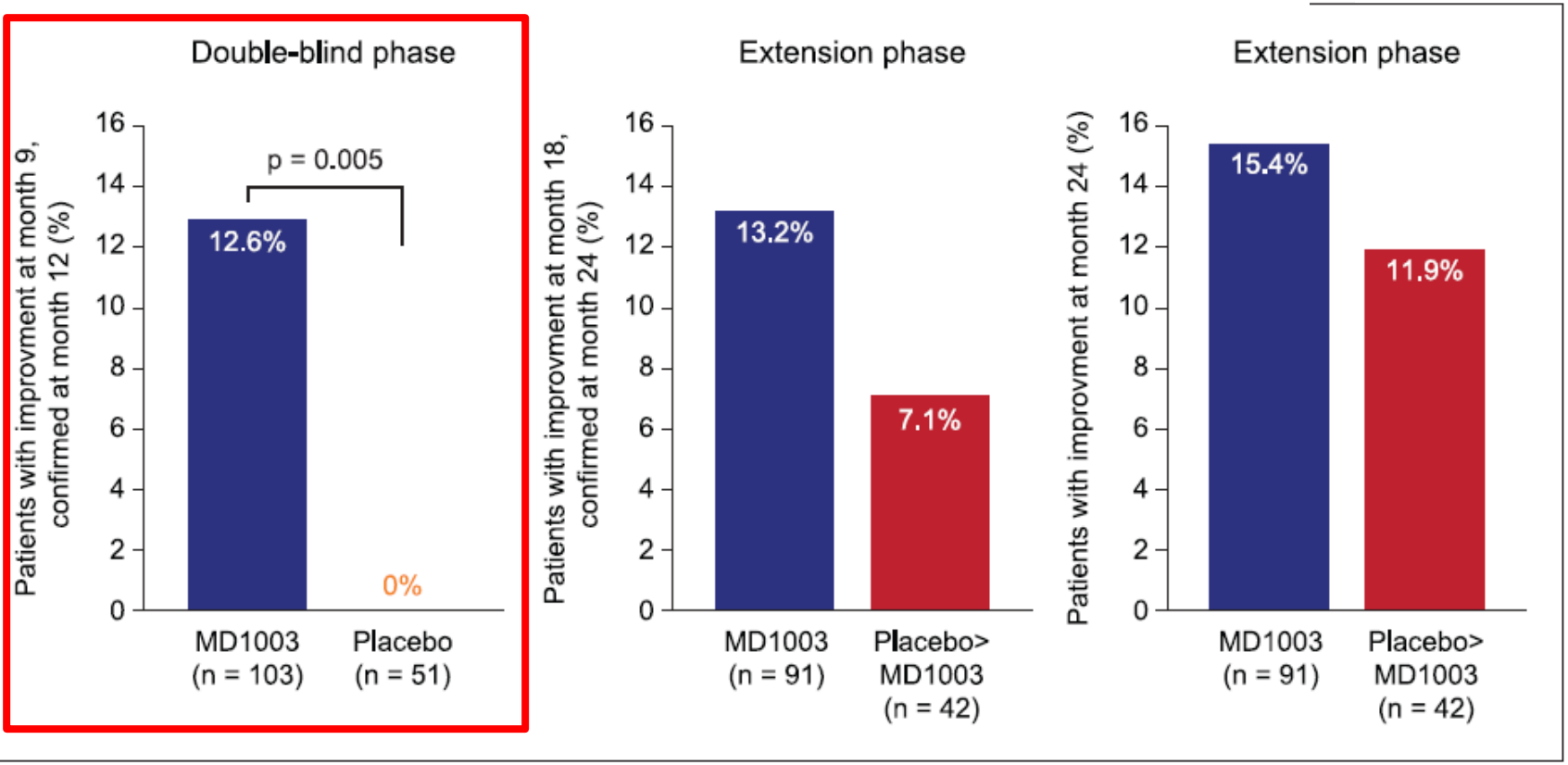
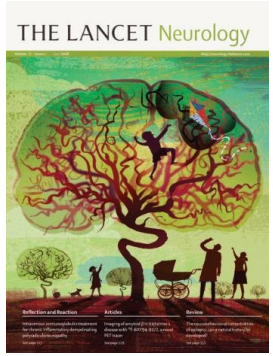


Figure 2. Proportion of patients with reversal of MS-related disability. Reversal of disability was defined as improvement of EDSS or TW25 values confirmed at the next visit (except for month 24 where no subsequent visit was available) compared with best respective values recorded at either the screening or the randomisation visits.
EDSS: Expanded Disability Status Scale; TW25: timed 25-foot walk.

Tourbah A et al, *Mult Scler*. 2016;22:1719-1731

Clemastine fumarate as a remyelinating therapy for multiple sclerosis (ReBUILD): a randomised, controlled, double-blind, crossover trial



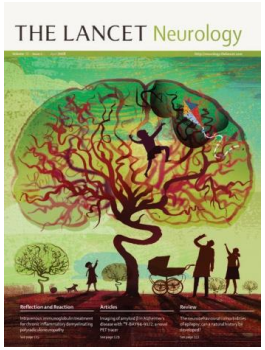
❖Myelin in the CNS is a specialised extension of the oligodendrocyte plasma membrane and clemastine fumarate can stimulate differentiation of oligodendrocyte precursor cells in vitro, in animal models, and in human cells

❖Single-centre, 150-day, double-blind, randomised, placebo-controlled, crossover trial in patients with relapsing multiple sclerosis with chronic demyelinating optic neuropathy on stable immunomodulatory therapy.

❖Patients were randomly assigned (1:1) to receive either clemastine fumarate (5·36 mg orally twice daily) for 90 days followed by placebo for 60 days (group 1), or placebo for 90 days followed by clemastine fumarate (5·36 mg orally twice daily) for 60 days (group 2).

❖The primary outcome was shortening of P100 latency delay on full-field, pattern-reversal, visual-evoked potentials.

Green AJ et al, *Lancet*. 2017;390:2481-2489



Clemastine fumarate as a remyelinating therapy for multiple sclerosis (ReBUILD): a randomised, controlled, double-blind, crossover trial

Clemastine fumarate treatment reduced the latency delay by 1·7 ms/eye (95% CI 0·5–2·9; p=0·0048)

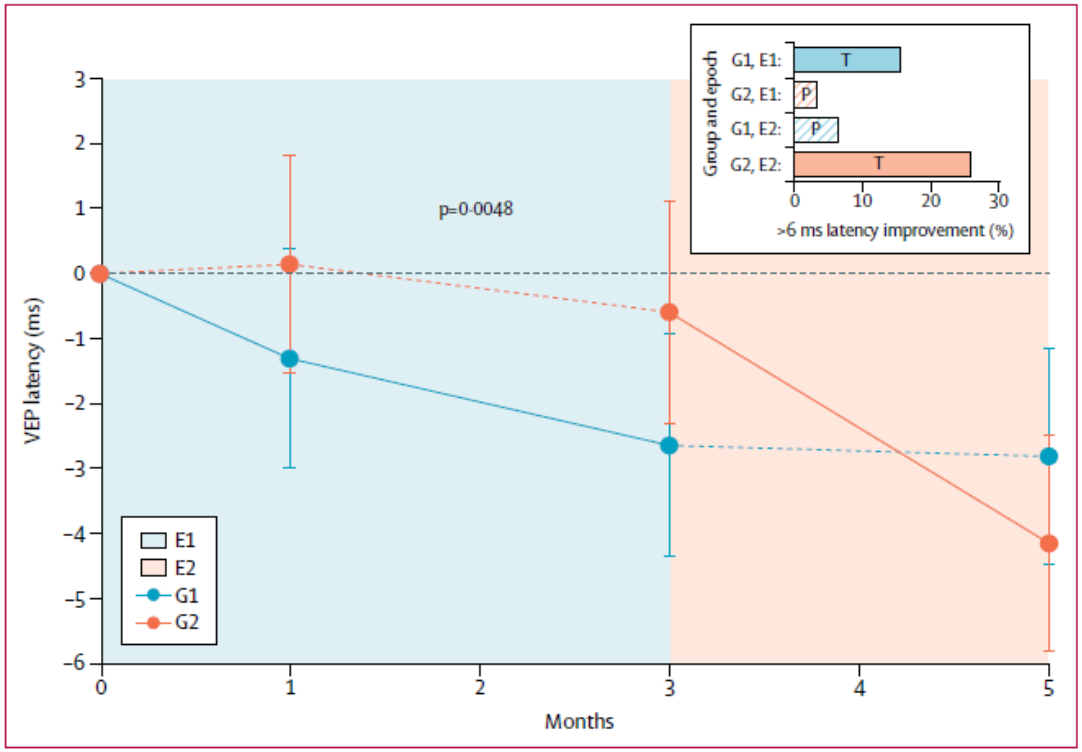


Figure 2: **Association of clemastine fumarate treatment with VEP latency delay in patients with chronic optic neuropathy**

Change from baseline in latency by group and epoch (model-derived estimates of means are represented by dots with the SE from baseline represented by error bars at each relevant timepoint). Solid line is on-treatment and dashed line is on-placebo. Blue line is group 1, orange line is group 2. Blue shaded area is epoch 1 and orange shaded area is epoch 2. p value is for primary analysis including crossover (with assumption of carryover). The inset is the percentage of patients with more than 6 ms improvement in latency delay. VEP=visual-evoked potential. G1=group 1. G2=group 2. E1=first epoch. E2=second epoch. T=treatment period. P=placebo period.

Green AJ et al, *Lancet*. 2017;390:2481-2489

....other mechanisms

Catania, Piazza Università

Trial of Minocycline in a Clinically Isolated Syndrome of Multiple Sclerosis

❖To determine whether minocycline reduces the risk of conversion from a first demyelinating event (also known as a clinically isolated syndrome) to multiple sclerosis.

❖ 70 patients received 1 00 mg of minocycline, administered orally twice daily, 70 patients received placebo.

❖The primary outcome was conversion to multiple sclerosis (diagnosed on the basis of the 2005 McDonald criteria) within 6 months after randomization.

❖The unadjusted risk of conversion to multiple sclerosis within 6 months after randomization was 61.0% in the placebo group and 33.4% in the minocycline group, a difference of 27.6 percentage points (95% confidence interval [CI], 11.4 to 43.9; P = 0.001).

Metz LM et al, *N Engl J Med* 2017; 376:2122-2133

Trial of Minocycline in a Clinically Isolated Syndrome of Multiple Sclerosis

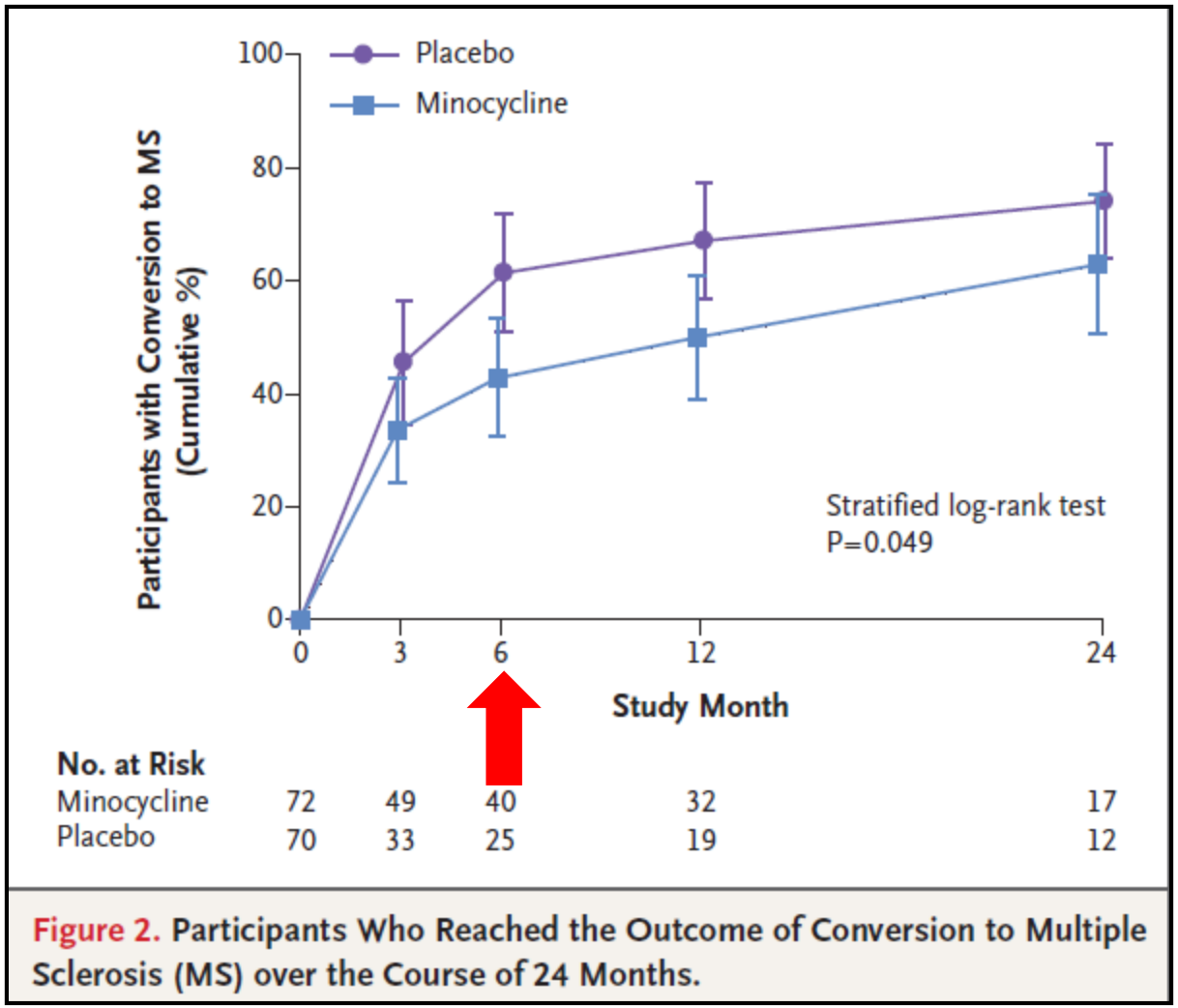


Figure 2. Participants Who Reached the Outcome of Conversion to Multiple Sclerosis (MS) over the Course of 24 Months.

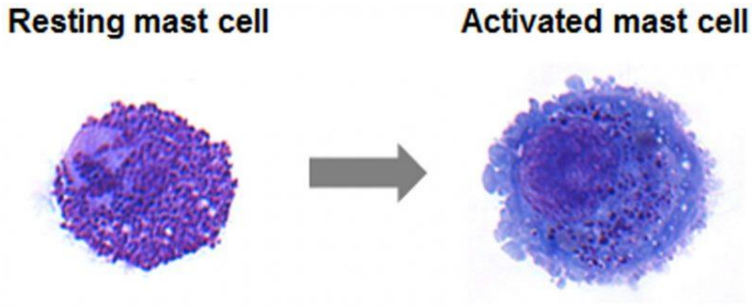
Metz LM et al, *N Engl J Med* 2017; 376:2122-2133

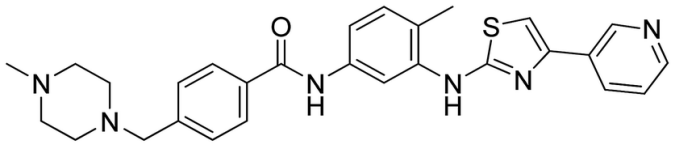
Masitinib treatment in patients with progressive multiple sclerosis: a randomized pilot study

❖Mast cells actively participate in the pathogenesis of MS, in part because they release large amounts of various mediators that sustain the inflammatory network.

❖Masitinib, a selective oral tyrosine kinase inhibitor, effectively inhibits the survival, migration and activity of mast cells.

❖Multicenter, randomized, placebo-controlled, proof-of-concept trial. Masitinib was administered orally at 3 to 6 mg/kg/day for at least 12 months. The primary response endpoint was the change relative to baseline in the multiple sclerosis functional composite score (MSFC).





Masitinib
Mol. Wt.: 498

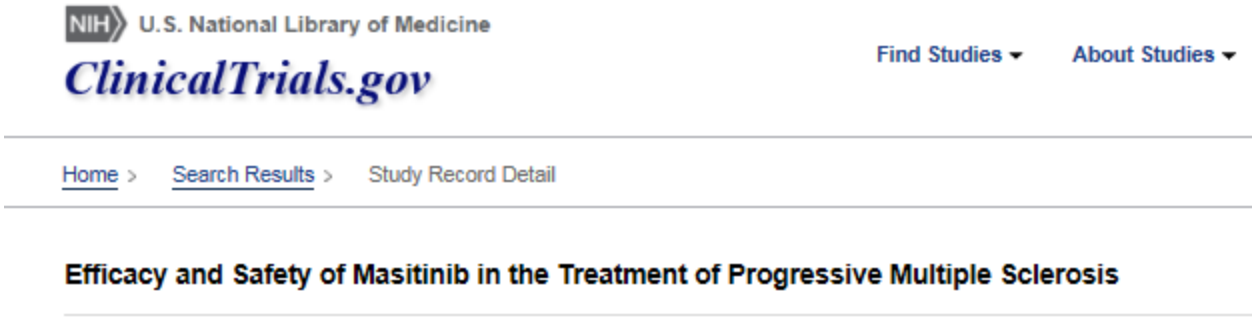
Vermersch P et al, *BMC Neurol*. 2012 Jun 12;12:36

Masitinib treatment in patients with progressive multiple sclerosis: a randomized pilot study

❖Masitinib appeared to have a positive effect on MS-related impairment for PPMS and SPMS patients, as evidenced by an **improvement in MSFC scores** relative to baseline, compared with a worsening MSFC score in patients receiving placebo; +103% ± 189 versus -60% ± 190 at month-12, respectively.

❖Positive effect of masitinib on MS-related impairment and potential retardation of disease progression for both PPMS and SPMS patients.

Vermersch P et al, *BMC Neurol*. 2012 ;12:36



In progress (**http://clinicaltrials.gov**,NCT01433497)

Relapsing / Remitting MS **Progressive MS** **Late Progressive MS**

Systemic Anti-Inflammatory Therapy,
Blockade of Immune Mediated
Tissue Injury

Neuroprotective Strategies,
(Microglia activation,
Oxidative Injury,
Mitochondrial
Protection)

Neuroprotective Strategies,
(Microglia Activation, Mitochondrial Protection),
Anti Inflammatory Therapy, Acting in the CNS

Age & Disease Duration

Lassmann H. *Mult Scler*. 2017;23:1593-1599

Catania, Archi della Marina

"D'ora in poi mi rivolgo solo al futuro perché ho deciso di passarci il resto della mia vita" (A. Einstein)