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Evidence for Improved Myelination in Patients Treated with Siponimod: Results from the Phase 3 EXPAND Magnetic Resonance Imaging Substudy

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Disclosures

Douglas L. Arnold has received honoraria from Acorda, Biogen Idec, Genentech, Genzyme, Novartis, F. Hoffmann-La Roche and Sanofi-Aventis; research support from Novartis and Biogen; and has an equity interest in NeuroRx Research, which performed the MRI analysis for the trial.

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Gavin Giovannoni is a steering committee member on the daclizumab trials for AbbVie, the BG12 and daclizumab trials for Biogen, the fingolimod and siponimod trials for Novartis, the laquinimod trials for Teva and the ocrelizumab trials for Roche. He has also received consultancy fees for advisory board meetings for oral cladribine trials for Merck KGaA and Sanofi-Genzyme, and in relation to DSMB activities for Synthon BV, as well as honoraria for speaking at the Physicians' summit and several medical education meetings. He is also the Co-Chief Editor of Multiple Sclerosis and Related Disorders (Elsevier).

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Background

- Magnetisation transfer ratio (MTR) reflects integrity of brain tissue structure, and changes in MTR are used as a marker of changes in myelin density in the brain[1,2]
- MTR decreases with acute demyelination and increases with remyelination[2-4]
- In preclinical studies, siponimod showed evidence of remyelinating effects[5,6]
- Siponimod significantly reduced the risk for confirmed disability progression and decline in cognitive processing speed in SPMS patients[7]

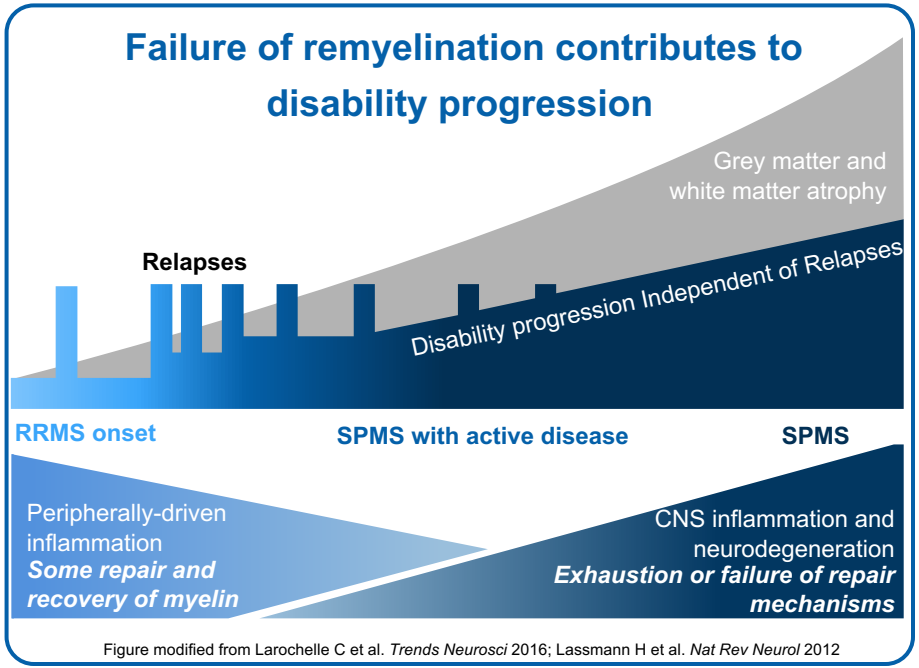


Figure modified from Larochelle C et al. *Trends Neurosci* 2016; Lassmann H et al. *Nat Rev Neurol* 2012

CNS, central nervous system; MTR, magnetisation transfer ratio; NAWM, normal-appearing white matter; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis

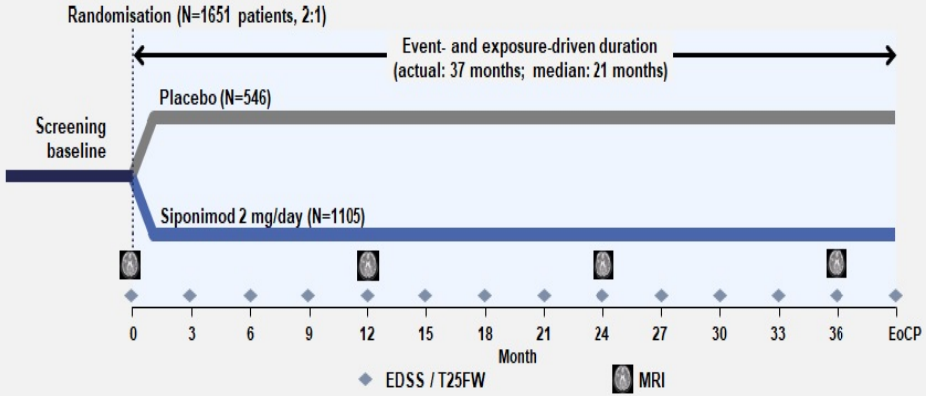
1. Filippi M et al. *Lancet Neurol*. 2019;18(2):198–210; 2. Arnold D et al. *J Neurol*. 2014; 261(12): 2429–37; 3. Deloire-Grassin MS et al. *J Neurol Sci.* 2000;178(1):10–~~16~~; 4. Merkler D et al.*NMR Biomed.* 2005;18(6):395–403; 5. Martin E et al. *ECTRIMS 2019*; P1376; 6. Mannioui A et al. *Mult Scler.* 2018; 24(11):1421–32; 7. Kappos et al. *Lancet.* 2018;391:1263–73.

Objective and Methods

Objective

To determine the effect of siponimod versus placebo on MTR changes in different brain regions and assess the degree of MTR recovery within MTR lesions

Randomised, double-blind, placebo-controlled, event- and exposure-driven study



MTR analysis included subset of EXPAND population (N=639; siponimod [n=413], placebo [n=226])

Assessments included:

MTR in tissues:
Absolute change from baseline in median normalised MTR (pu) at M12 and M24 in:
- **NABT**
- **cGM**
- **NAWM**

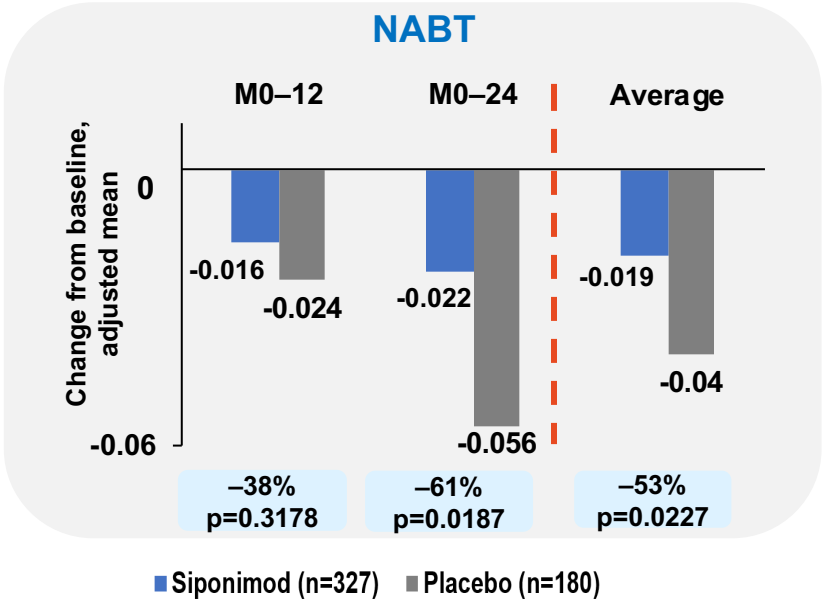
+

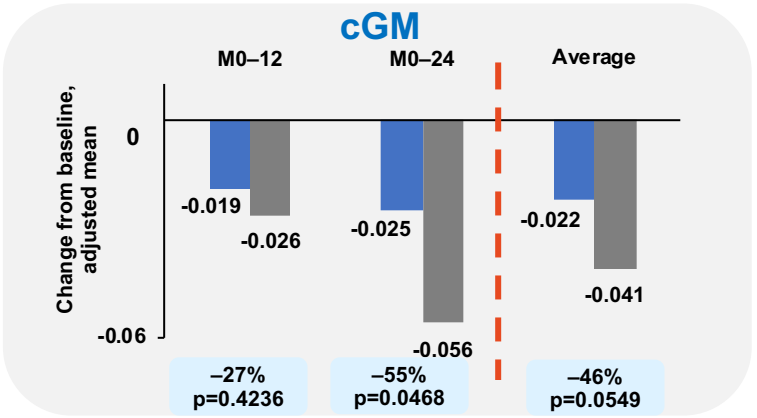
Lesional MTR:

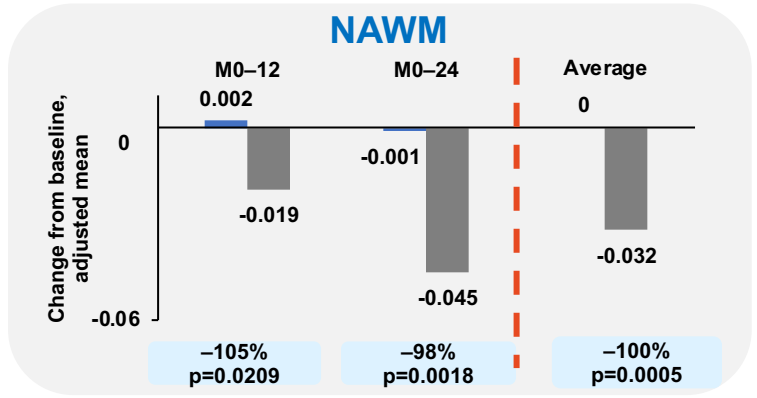
MTR recovery metrics
assessed in newly formed MTR lesions

cGM, cortical grey matter; EDSS, Expanded Disability Status Scale; EoCP, end of core phase; M, month; MRI, magnetic resonance imaging; MTR, magnetisation transfer ratio; N, total number of patients; n, number of patients; NABT, normal-appearing brain tissue; NAWM, normal-appearing white matter; pu, percent unit; T25FW, Timed 25-Foot Walk

Effect of Siponimod on Changes in Median nMTR in NABT, cGM and NAWM (FAS)



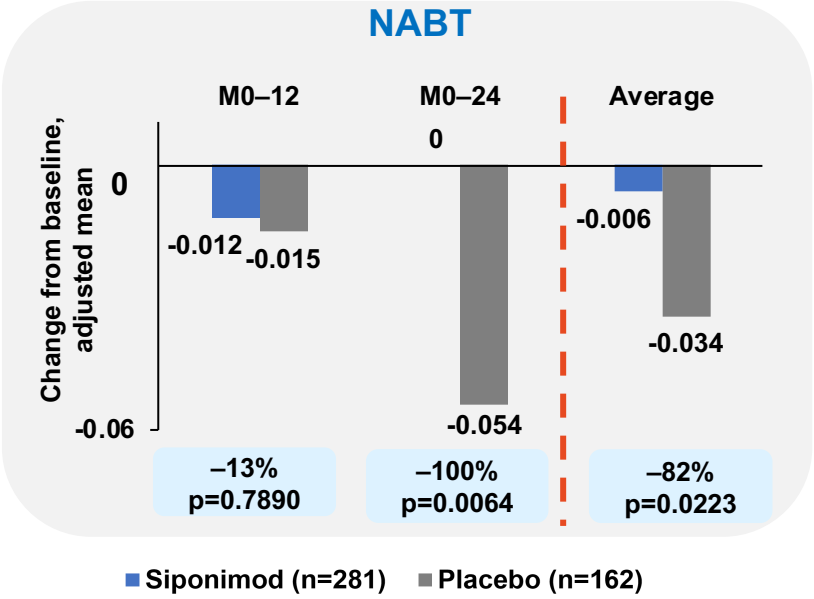


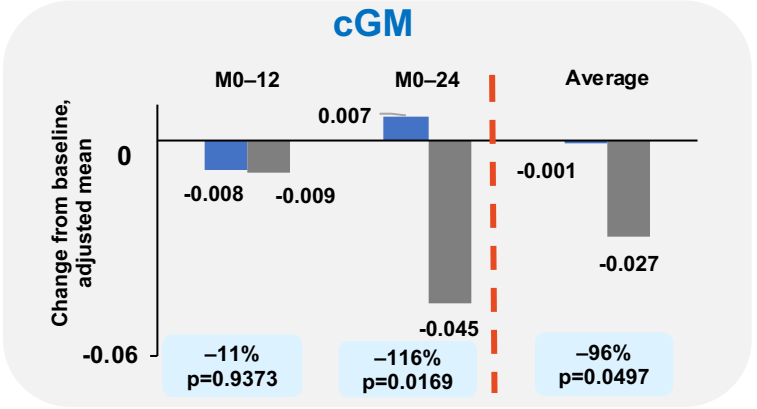


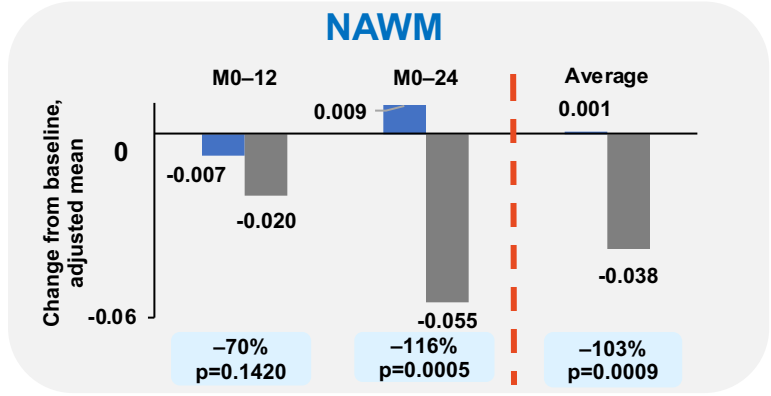
The FAS included all randomized patients with assigned treatments who took at least one dose of study medication

cGM, cortical grey matter; FAS, full analysis set; M, month; n, number of patients included in the analysis (i.e. with at least one post-baseline result); NABT, normal-appearing brain tissue; NAWM, normal-appearing white matter; nMTR, normalised magnetisation transfer ratio

Effect of Siponimod on Changes in Median nMTR in NABT, cGM and NAWM (PPS)







The PPS included all patients from FAS who do not have any major protocol deviations that could confound the interpretation of analyses conducted on the FAS, notably data after switch to a rescue medication were excluded from this analysis

cGM, cortical grey matter; M, month; n, number of patients included in the analysis (i.e. with at least one post-baseline result); NABT, normal-appearing brain tissue; NAWM, normal-appearing white matter; nMTR, normalised magnetisation transfer ratio; PPS, per protocol set

MTR Lesion Detection Timepoints and Number of Lesions

At least 3 MTR-MRI scans were needed to obtain:

- A stable pre-lesion MTR value
- Detect acute newly-forming lesion
- A stable post-lesion MTR value

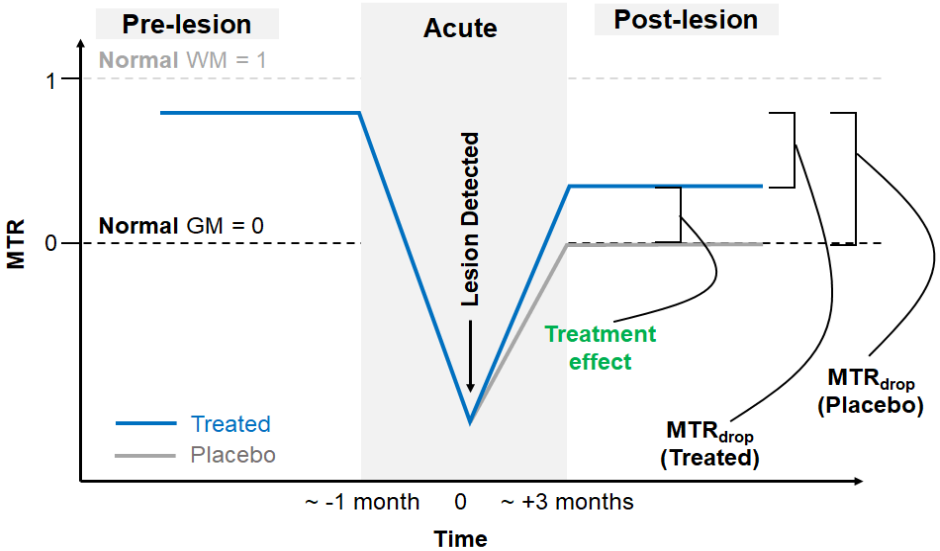
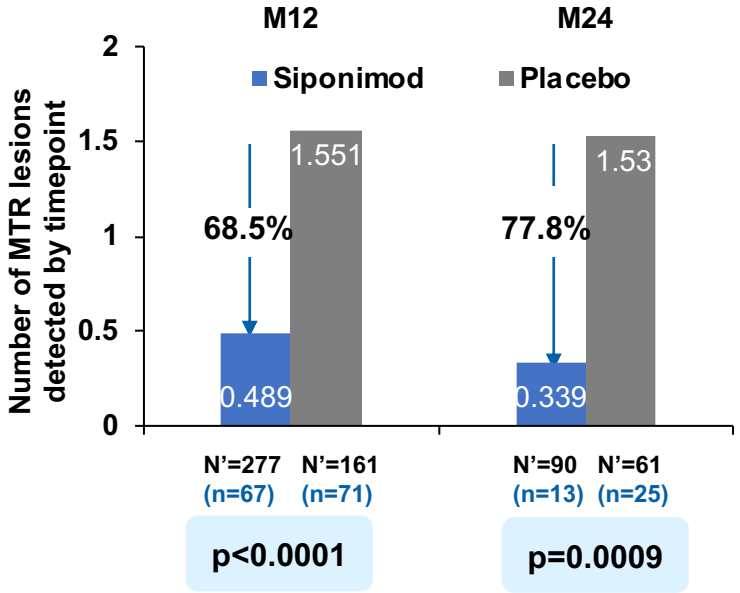


Figure adapted from Brown et al 2013 Neuroimaging

Number of MTR lesions detected by timepoint (FAS)

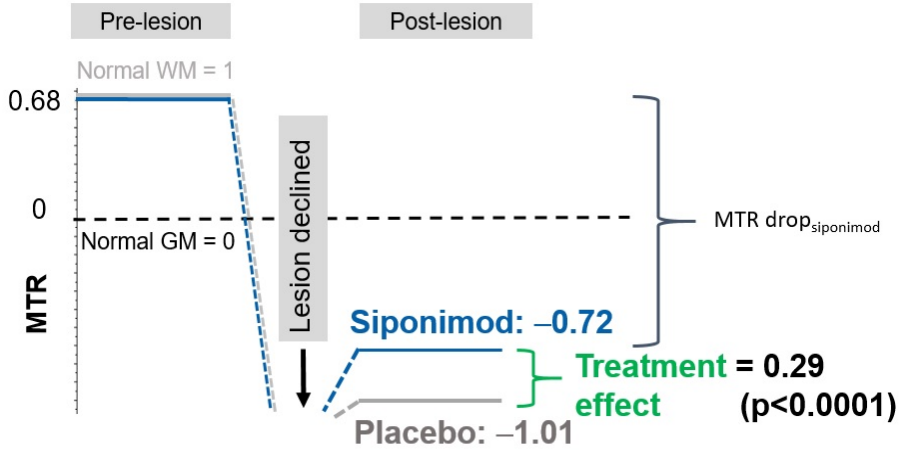


N', number of patients included in analysis (i.e. with at least 3 MRI scans)
n, number of patients with MTR lesion amongst those included in analysis

FAS, full analysis set; GM, grey matter; M, month; MTR, magnetisation transfer ratio; MRI, magnetic resonance imaging; WM, white matter

MTR Recovery Metrics in MTR Lesions

Constrained multilevel model accounting for lesion volume



Pre-lesion value: A stable pre-lesion MTR value
Post-lesion value: A stable post-lesion MTR value

Unconstrained multilevel model	Siponimod (N=413, N'=72)	Placebo (N=226, N'=80)	Treatment difference (siponimod vs placebo)	p-value
MTR drop*	–1.321	–1.506	**0.185**	**0.0036**
MTR drop* accounting for lesion volume	–1.351	–1.707	**0.356**	**<0.0001**
Constrained multilevel model	**Siponimod (N=413, N'=72)**	**Placebo (N=226, N'=80)**	**Treatment difference (siponimod vs placebo)**	**p-value**
MTR drop* accounting for lesion volume	–1.396	–1.687	**0.290**	**<0.0001**

Data presented as adjusted means

*MTR drop (i.e. MTR recovery metrics) describes the total decrease in normalized MTR from pre- to post-MTR lesion timepoints, The latest available time-point prior to new lesion formation was taken as pre-lesion time-point. The latest available time-point post new lesion formation will be taken as the post-lesion time-point

- Siponimod treatment showed improved MTR recovery within newly formed MTR lesions versus placebo

GM, grey matter; N, total number of patients; MTR, magnetisation transfer ratio; MRI, magnetic resonance imaging; WM, white matter

Summary

- **Siponimod demonstrated a consistent and significant effect on the decrease of MTR over time across NABT, cGM and NAWM versus placebo:**
  - The effect was most pronounced at M24 and in NAWM, a decrease in MTR appeared to be suppressed completely
- **In addition to reducing grey matter loss and BVL overall, siponimod improved MTR recovery in newly formed lesions, an effect that could be consistent with promotion of remyelination observed previously in preclinical studies**
  - For the EXPAND grey matter atrophy ePresentation, please refer to EPR3098 by Prof. Fox
- **Results suggest that siponimod demonstrates a central effect on myelin repair mechanism, corroborating findings from the preclinical studies[1,2]**

BVL, brain volume loss, cGM, cortical grey matter; M, month; MTR, mangetisation transfer ratio; NABT, normal-appearing brain tissue; NAWM, normal-appearing white matter

1. Martin E et al. *ECTRIMS 2019*; P1376; 2. Mannioui A et al. *Mult Scler.* 2018; 24(11):1421–32.