

Original Research Paper

Effect of siponimod on magnetic resonance imaging measures of neurodegeneration and myelination in secondary progressive multiple sclerosis: Gray matter atrophy and magnetization transfer ratio analyses from the EXPAND phase 3 trial

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Abstract

Background: Magnetic resonance imaging (MRI) measurements of gray matter (GM) atrophy and magnetization transfer ratio (MTR; correlate of myelination) may provide better insights than conventional MRI regarding brain tissue integrity/myelination in multiple sclerosis (MS).

Objective: To examine the effect of siponimod in the EXPAND trial on whole-brain and GM atrophy, newly formed normalized magnetization transfer ratio (nMTR) lesions, and nMTR-assessed integrity of normal-appearing brain tissue (NABT), cortical GM (cGM), and normal-appearing white matter (NAWM). **Methods:** Patients with secondary progressive multiple sclerosis (SPMS) received siponimod (2 mg/day; n=1037) or placebo (n=523). Endpoints included percentage change from baseline to months 12/24 in whole-brain, cGM, and thalamic volumes; change in nMTR from baseline to months 12/24 in NABT, cGM, and NAWM; MTR recovery in newly formed lesions.

Results: Compared with placebo, siponimod significantly reduced progression of whole-brain and GM atrophy over 12/24 months, and was associated with improvements in brain tissue integrity/myelination within newly formed nMTR lesions and across NABT, cGM, and NAWM over 24 months. Effects were consistent across age, disease duration, inflammatory activity subgroups, and disease severity.

Conclusion: Siponimod reduced brain tissue damage in patients with SPMS as evidenced by objective measures of brain tissue integrity/myelination. This is consistent with central nervous system (CNS) effects observed in preclinical models. ClinicalTrials.gov number: NCT01665144.

Keywords: Secondary progressive multiple sclerosis, MRI, magnetization transfer ratio, gray matter, brain integrity, myelination, siponimod

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Introduction

Multiple sclerosis (MS) is a chronic, inflammatory, demyelinating, neurodegenerative disease of the central nervous system (CNS). At disease onset, most patients (~85%) receive a diagnosis of relapsing-remitting multiple sclerosis (RRMS) and 25%–40% advance to secondary progressive multiple sclerosis (SPMS) within 10 years.^{1,2}

RRMS is characterized by relapses with full or partial recovery followed by periods of remission, with pathophysiology apparently driven primarily by peripherally mediated focal inflammation.^{3,4} SPMS is distinguished from RRMS by disability progression independent of relapses.^{1,2,5} In SPMS, relapses become less frequent over time; approximately 30% of patients experience relapses, most of which occur Multiple Sclerosis Journal

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Mellen Center for Multiple Sclerosis Treatment and Research, Neurological Institute, Cleveland Clinic, Cleveland, OH, USA within 5 years of SPMS onset and/or before the age of 55 years.⁵ SPMS pathophysiology is not fully characterized but is believed to involve chronic inflammation compartmentalized in the CNS and failure or exhaustion of myelin repair mechanisms.^{3,4} In addition to compartmentalized inflammation, a loss of compensatory reserve capacity may be relevant for the emergence of clinical progression in the absence of relapses.⁶

Conventional T2- and T1-weighted magnetic resonance imaging (MRI) has been very revealing of the peripherally mediated focal inflammation that underlies relapses in MS, but less so of the compartmentalized inflammation more closely associated with progression. The latter requires quantitative analysis methods to detect accelerated rates of global and regional brain volume loss (e.g. gray matter (GM) volume loss), and changes within lesional and normal-appearing tissues, such as myelin loss and repair. However, MRI measurements of total brain volume loss do not provide specific information on disease pathophysiology because small changes may be caused by several processes, including neuronal/ axonal loss, demyelination, and inflammation.7 MRI measurements of GM atrophy and magnetization transfer ratio (MTR) may provide better insights into different pathological pathways involved in neurodegeneration in SPMS. Cortical gray matter (cGM) and thalamic volume loss are also associated with longterm disability accumulation and cognitive decline.8-10 GM atrophy is also linked to neurodegenerative worsening in progressive disease beyond the relapsing, inflammation-driven processes that occur earlier in MS.^{11–14} Since myelin is the primary target of inflammation in MS, the measurement of changes in myelin content is also of particular interest. This can be accomplished on clinical scanners using MTR imaging. Change in MTR has been shown to be a marker of myelin density in the brain.15

Siponimod is an oral sphingosine 1-phosphate (S1P) receptor modulator that selectively binds to S1P₁ and S1P₅ receptors.¹⁶ Indications for siponimod vary; it is approved in Europe in adults with active SPMS (i.e. with relapses or imaging features of disease activity),¹⁶ in the United States in relapsing forms of MS, including clinically isolated syndrome, RRMS, and active SPMS,¹⁷ and in some countries (e.g. Australia and Japan), in all patients with SPMS.

Clinical and preclinical evidence supports a dual mechanism of action for siponimod. Peripherally mediated anti-inflammatory effects through the $S1P_1$ receptor reduce the egress of pathogenic lymphocytes

from lymph nodes, limiting the number of circulating lymphocytes entering the CNS.¹⁸ Preclinical data also suggest direct anti-inflammatory and promyelination effects of siponimod acting via the S1P₁ and S1P₅ receptors on CNS-resident cells, including astrocytes, microglia, and oligodendroglial cells.^{19–23}

In the phase 3 EXPAND study, siponimod was investigated in a broad population with SPMS (Expanded Disability Status Scale (EDSS) score of 3.0-6.5), including patients with advanced disease (>50%) required walking aids at study entry (EDSS ≥ 6.0)).²⁴ Compared with placebo, siponimod significantly reduced: the risk of 3-month confirmed disability progression (assessed by EDSS) by 21% and of 6-month progression by 26%;24 the risk of meaningful worsening in cognitive processing speed (determined as a ≥4-point decline in the Symbol Digit Modalities Test (SDMT) score);^{16,24,25} and total brain volume loss.²⁴ In addition, a significant effect was also observed on measures of inflammatory disease activity, including reduction in annualized relapse rate by 55%, MRI T2 and T1 gadolinium lesion activity by 81% and 86%, respectively, and a significant reduction in T2 lesion volume.24

Given the efficacy of siponimod on clinical measures of progression, any effects on GM atrophy and MTR may give further insights into its dual mechanisms of action. Currently, little evidence exists on the impact of disease-modifying therapies (DMTs) on regional atrophy and MTR outcomes in populations with SPMS. One previous study observed no overall effect of interferon β 1b on the worsening of MTR measures.²⁶ Some evidence also exists in populations with RRMS, with previous studies having shown effects of dimethyl fumarate and alemtuzumab.^{27,28} Overall, more information is needed from large-scale studies to assess the impact of specific DMTs on these MRI measures, especially in patients with progressive MS.

Using data from EXPAND, we assessed the effect of siponimod versus placebo on cortical and thalamic GM atrophy, as well as changes in normalized magnetization transfer ratio (nMTR) measurements in normal-appearing brain tissue (NABT), cGM, and normal-appearing white matter (NAWM), and newly formed nMTR lesions in a population with SPMS.

Methods

Trial design and patients

The EXPAND (NCT01665144) study methodology was reported.²⁴ In brief, EXPAND was a phase 3,

randomized, double-blind, placebo-controlled, eventand exposure-driven study of up to 37 months' duration (median [interquartile range]=21.3 [15.5–27.0] months) investigating the efficacy and safety of siponimod in patients with SPMS. Patients were randomized (2:1) to once-daily oral siponimod 2 mg or placebo. Key eligibility criteria included age 18–60 years, a diagnosis of SPMS, EDSS score of 3.0–6.5 at screening, a history of RRMS, documented EDSS score progression in the past 2 years, and no evidence of relapses in the previous 3 months. The protocol was approved by the relevant institutional review board or ethics committee at each trial site; all patients provided written informed consent.

Procedures

At all sites, standard-resolution MRI scans (1 mm \times 1 mm \times 3 mm) were scheduled at screening, at months 12, 24, and 36, and at the end of the controlled treatment phase (end of study (EOS) scan; if different from annual visits). MRI scans were also conducted in patients who discontinued prematurely from the double-blind study period and/or study treatment (end of treatment (EOT) scan).

Either MTR $(1 \text{ mm} \times 1 \text{ mm} \times 3 \text{ mm})$ or high-resolution (1 mm isotropic) T1-weighted MRI sequences were added to conventional MRI scans at centers meeting prespecified technical requirements. MRI data were analyzed independently at a central site (NeuroRx Research, Montreal, QC, Canada) by staff blinded to treatment assignment.

Percentage brain volume change, percentage cGM volume change, and thalamic volume change were measured from baseline to each follow-up time point (i.e. at month 12, month 24, EOT, and EOS) using the paired Jacobian integration.²⁹ GM atrophy was initially measured in the cohort of patients with highresolution MRI scanning. This was because of theoretical concerns about partial volume effects when assessing smaller and more complex brain structures, such as the thalamus and hippocampus. However, review of the results from the standard- and high-resolution MRI scans showed that the effects of the different scanning protocol were small. All patients underwent standard-resolution MRI scans; however, for those patients who also underwent highresolution MRI scans, GM atrophy measures were only processed from high-resolution MRI scans to avoid double-counting. The combined MRI set comprised both the standard- and high-resolution sets. Full details on the acquisition methodologies and scanners are provided in the Supplementary Appendix and MRI Appendix documents.

Objectives and endpoints

The objectives of the EXPAND analysis described here were to evaluate the effect of siponimod versus placebo on total brain volume (secondary objective), cGM and thalamic volume, and nMTR (exploratory objectives).

The following endpoints were assessed: percentage change from baseline to months 12 and 24 in total brain volume, cGM volume, and thalamic volume; change in nMTR from baseline to months 12 and 24 in NABT, cGM, and NAWM; and nMTR recovery in newly formed MTR lesions (i.e. new areas of decreased MTR defined on MTR images at month 12 in most cases, or at month 24 if a subsequent scan was available at month 36), which may reflect remyelination, assessed by the change in stable nMTR from pre- to post-lesion time points.

Statistical analyses

Analyses were performed for both the full analysis set (FAS) and per-protocol set (PPS). The FAS included all randomized patients with assigned treatments who received ≥ 1 dose of study drug; the PPS included all patients in the FAS, except those with major protocol deviations or with efficacy data collected after permanent study drug discontinuation. A greater focus was placed on analyses in the PPS because potentially confounding data from patients who switched from placebo to open-label siponimod as rescue medication were not included in the PPS.²⁴ FAS analyses are included in the Supplementary Appendix.

In these analyses, the EOT and EOS scans, which are not time point-specific, were remapped to one of the scheduled time points (i.e. month 12, 24, or 36). Percentage change in total brain, cGM, and thalamic volumes were analyzed using a repeated-measures model adjusted for treatment, visit, normalized brain volume, number of baseline gadolinium-enhancing lesions, baseline T2 lesion volume, and visit-by-treatment and visit-by-baseline brain volume interactions. An unstructured covariance matrix was used in the repeated-measures model to account for the variance in percent volume change at each time point and covariance between time points. These analyses were performed in patients with high-resolution scans and in patients with standard-resolution scans. Analyses for the combined MRI cohort were also conducted. The consistency of the treatment effect in patients with high- versus standard-resolution scans was further evaluated using subgroup- (high vs standard) by-treatment interaction tests. This analysis did not evidence heterogeneity between subgroups (Supplemental Table S1).

In the combined MRI cohort, cGM volume and thalamic volume were analyzed in subgroups stratified by baseline age (\leq 45 years or >45 years), disease duration (\leq 15 years or >15 years), EDSS score (<6.0 or \geq 6.0), SDMT score (\leq 43 or >43), and SPMS activity (active SPMS was defined as \geq 1 relapse in the 2 years before screening and/or \geq 1 gadoliniumenhancing lesion at baseline).

MTR was analyzed in the MTR patient cohort. Variations in MTR acquired on different scanners were reduced by MTR normalization, by setting the MTRs of high-confidence cGM to 0 and of high-confidence white matter to 1 on the MTR scan of a healthy control individual on the same scanner. A repeated-measures model, accounting for within-patient correlation, was used to obtain nMTR estimates in NABT, cGM, and NAWM. The model was adjusted for treatment, visit, baseline median nMTR of respective brain tissue, baseline number of gadolinium-enhancing lesions, baseline T2 lesion volume, and visit-by-treatment and visit-by-baseline interactions.

Lesional nMTR recovery was assessed in new nMTR lesions¹¹ by comparing nMTR decrease from postlesion to pre-lesion time points for siponimod versus placebo. Of note, at least three nMTR scans were required to assess lesional nMTR recovery (prelesion, peri-lesion, and post-lesion). Considering the duration of the study, the majority of peri-lesional scans were obtained at the month 12 visit (or remapped month 12 visit). The latest available measurements before and after the formation of a new lesion were considered. Given the yearly scans, these measurements represented stable pre- and post-lesion MTR values because the period of acute lesion recovery lasts approximately 4 months. Results were analyzed in the FAS by a multilevel model that accounted for within-lesion and within-patient correlations. The model was adjusted for treatment, lesion time points, age, and treatment-by-time point interaction. Lesion volume was used as a weighting factor, and estimates were derived for pre-lesional and post-lesional time points. A model including all possible measurements at any time point (i.e. pre-lesional, new lesion, and post-lesional) was also derived.

Results

Patient characteristics

In total, GM volume measurements were analyzed from 546 patients (siponimod, n=376; placebo, n=170) who underwent high-resolution MRI scans and from 1007 patients (siponimod, n=656; placebo, n=351) with standard-resolution MRI scans. The subset for MTR analyses included 606 patients (siponimod, n=388; placebo, n=218). Baseline demographic and disease characteristics were broadly similar across all subsets of patients and the overall EXPAND population (Table 1).

GM atrophy analyses

In the combined MRI cohort, siponimod slowed cGM (with consistent effects in the high- and standardresolution MRI patient subsets (Supplemental Table S2)), thalamic, and total brain volume loss versus placebo after 12 and 24 months of treatment (PPS; Figure 1).

Adjusted mean percentage changes in cGM volume from baseline to month 12 were 0.01 for siponimod and -0.60 for placebo (102% relative reduction in volume loss; p < 0.0001); corresponding changes from baseline to month 24 were -0.39 for siponimod and -1.04 for placebo (63% relative reduction in volume loss; p < 0.0001; Figure 1(a)). Adjusted mean percentage changes in thalamic volume from baseline to month 12 were -0.47 for siponimod and -0.94 for placebo (50% relative reduction in volume loss; p < 0.0001); corresponding changes from baseline to month 24 were -1.02 for siponimod and -1.77 for placebo (42% relative reduction in volume loss; p < 0.0001; Figure 1(b)). Adjusted mean percentage changes in total brain volume from baseline to month 12 were -0.23 for siponimod and -0.45 for placebo (49% relative reduction in volume loss; p < 0.0001); corresponding changes from baseline to month 24 were -0.62 for siponimod and -0.90 for placebo (31% relative reduction in volume loss; p < 0.0001; Figure 1(c)). The effects of siponimod versus placebo on cGM, thalamic, and total brain atrophy were consistent in the FAS (Supplemental Figure S1).

Although the rate of cGM atrophy was constant/similar across subgroups, the rate of thalamic atrophy was more pronounced in the group of patients with inflammatory disease activity (i.e. gadolinium-enhancing lesions). Nevertheless, reductions from baseline to months 12 and 24 in cGM and thalamic atrophy with siponimod versus placebo were consistent across patient subgroups, regardless of baseline age, disease

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	Standard-resolutior $(N=1007)$	n MRI subset	High-resolution MR	I subset (N=546)	MTR subset (N =600	()	Overall EXPAND ((combined MRI) ()	population ^b V=1560)
	Siponimod $(n = 656)$	Placebo $(n=351)$	Siponimod $(n=376)$	Placebo $(n=170)$	Siponimod $(n=388)$	Placebo $(n=218)$	Siponimod $(n = 1037)$	Placebo $(n=523)$
Age, years, mean (SD)	48.0 (7.5)	48.4 (8.0)	47.6 (8.4)	48.0 (7.5)	48.0 (7.5)	48.0 (8.3)	47.9 (7.9)	48.2 (7.9)
Women, n (%)	396 (60.4)	209 (59.5)	231 (61.4)	101 (59.4)	238 (61.3)	129 (59.2)	631 (60.8)	310 (59.3)
Duration of MS since first symptom, years, mean (SD)	17.1 (8.4)	16.1 (8.5)	16.8 (8.2)	16.6 (7.8)	16.7 (8.1)	16.2 (8.7)	17.0 (8.3)	16.2 (8.3)
Time since conversion to SPMS, years, mean (SD)	3.6 (3.3)	3.2 (3.2)	4.1 (3.9)	4.0 (3.2)	3.5 (3.3)	3.1 (3.2)	3.8 (3.5)	3.5 (3.2)
Baseline EDSS score, median (range)	6.0 (2.5–6.5)	6.0 (2.5–7.0)	6.0 (2.5–7.0)	6.0 (3.0–6.5)	6.0 (2.5–6.5)	6.0 (2.5–7.0)	6.0 (2.5–7.0)	6.0 (2.5–7.0)
SDMT score, mean (SD)	39.5 (13.7)	39.9 (13.6)	37.5 (14.3)	38.0(13.1)	39.6 (13.3)	40.3 (13.3)	38.8 (14.0)	39.3 (13.4)
Normalized brain volume, cm ³ , mean (SD)	1434.0 (81.2)	1431.9 (86.0)	1403.4 (92.0)	1405.2 (87.1)	1430.3 (80.5)	1434.1 (89.7)	1422.7 (86.5)	1423.5 (87.3)
Cortical gray matter volume, cm ³ , mean (SD)	514.4 (49.4)	511.5 (56.8)	542.3 (56.0)	542.8 (52.3)	516.2 (47.7)	512.9 (55.6)	524.3 (53.5)	521.6 (57.3)
Thalamic volume, cm ³ , mean (SD)	13.9 (1.9)	13.9 (1.9)	14.0 (2.1)	14.1 (1.9)	14.0 (1.8)	14.0 (1.9)	13.9 (2.0)	13.9 (1.9)
Patients with ≥ 1 Gd+ T1 lesion at baseline, n (%)	133 (20.9)	69 (20.2)	94 (25.8)	37 (22.6)	77 (20.4)	39 (18.6)	227 (22.6)	107 (21.1)
T2 lesion volume, cm ³ , mean (SD)	15.1 (16.1)	14.3 (15.9)	16.7 (16.9)	15.7 (15.2)	14.3 (15.1)	14.2 (15.9)	15.7 (16.4)	14.7 (15.7)
EDSS: Expanded Disability Status set; SD: standard deviation; SDM PPS included all patients from the "Seven patients from the overall E.	Scale; FAS: full analys F: Symbol Digit Modalit FAS who did not have XPAND population did	is set; Gd+: gadolinium-e ies Test; SPMS: secondar any major protocol deviat not have any GM measure	mhancing; GM: gray matt y progressive multiple sel ions that could confound i ement and accordingly are	er; MRI: magnetic resonan erosis. interpretation. : not included in the high-n	ce imaging; MS: multiple ssolution nor in the stands	: sclerosis; MTR: magnet urd-resolution set.	tization transfer ratio; P	PS: per-protocol



Figure 1. Percentage change in volume of (a) cGM, (b) thalamus, and (c) total brain in the combined MRI cohort (PPS^a).

cGM: cortical gray matter; CI: confidence interval; FAS: full analysis set; Gd+: gadolinium-enhancing; LS: least-squares; M, month; MMRM: multilevel model for repeated measures; MRI, magnetic resonance imaging; PPS: per-protocol set. Percentage changes in brain structure volumes from baseline were analyzed using an MMRM adjusted for visit, treatment, baseline brain volume of a specific region, number of Gd+ T1 lesions at baseline, T2 lesion volume at baseline, treatment-by-visit interaction, and baseline total brain volume-by-visit interaction. ^aPPS included all patients from the FAS who did not have any major protocol deviations that could confound interpretation. duration, activity, or severity (based on EDSS and SDMT baseline scores) in both the PPS (Figures 2 and 3) and the FAS (data not shown).

MTR analyses

In the MTR subset, siponimod was associated with an increase in nMTR from baseline or return to baseline levels in all brain tissues evaluated. These effects were evident at month 24 (PPS; Figure 4).

There were no significant differences in mean nMTR change from baseline to month 12 with siponimod versus placebo in NABT (-0.011 vs -0.014; betweentreatment difference: 21%; p=0.7285), cGM (-0.007) vs -0.009; between-treatment difference: 22%; p = 0.8308), or NAWM (-0.005 vs -0.018; betweentreatment difference: 72%; p=0.1550). However, by month 24, mean nMTR had increased above baseline levels with siponimod, but had continued to decrease in all tissues with placebo (mean nMTR changes for siponimod vs placebo: NABT, 0.001 vs -0.055; between-treatment difference: 102%; p=0.0050; cGM, 0.008 vs -0.046; between-treatment difference: 117%; p=0.0141; NAWM, 0.010 vs -0.056; between-treatment difference: 118%; p=0.0004); the average of the between-treatment differences at months 12 and 24 for NABT, cGM, and NAWM was in the range 85%-105% (Figure 4). The effect of siponimod versus placebo on reduction or suppression of nMTR decrease over time was consistent in the PPS and the FAS (Supplemental Figure S2).

Compared with placebo, siponimod reduced or suppressed nMTR decrease over time across all patient subgroups (baseline age, disease duration, severity, or activity) in both the PPS (Figure 5) and FAS (data not shown), although the differences did not always reach nominal statistical significance. The magnitude of the between-treatment differences varied across subgroups: from 70% to 170% for NABT (Figure 5(a)); from 59% to 188% for cGM (Figure 5(b)); and from 81% to 195% for NAWM (Figure 5(c)).

In newly formed nMTR lesions, siponimod was associated with improved nMTR recovery versus placebo. Total decrease in nMTR from stable pre-lesion to stable post-lesion values was less with siponimod than placebo (-1.35 vs -1.71; between-treatment difference: 0.36; p < 0.0001) (Table 2). This model was based on the latest pre-lesion and latest post-lesion measurements. Similar results were obtained using a multilevel model with all pre-lesion, new lesion, and post-lesion time points included (Figure 6).

Subgroups		Placebo	Siponimod		(siponimod/ placebo)	difference (95% CI)	placebo (p value)
Age ≤ 45 years		-0.61		0.10	246/120	0.72 (0.53, 0.91)	118 (p < 0.0001)
Age > 45 years		-0.60	-0.04		446/217	0.55 (0.41, 0.69)	92 (<i>p</i> < 0.0001)
Disease duration ≤ 15 years		-0.57		0.05	318/171	0.63 (0.47, 0.79)	111 (<i>p</i> < 0.0001)
Disease duration > 15 years		-0.63	-0.03		374/165	0.60 (0.44, 0.76)	95 (<i>p</i> < 0.0001)
EDSS < 6.0		-0.59		0.02	319/165	0.60 (0.44, 0.77)	102 (p < 0.0001)
EDSS ≥ 6.0		-0.61		0	373/172	0.62 (0.46, 0.77)	102 (p < 0.0001)
SDMT > 43		-0.49		0.08	299/159	0.57 (0.40, 0.73)	116 (<i>p</i> < 0.0001)
SDMT ≤ 43		-0.68	-0.05		387/176	0.64 (0.48, 0.79)	94 (<i>p</i> < 0.0001)
Non-active SPMS		-0.53 l		0.04	344/167	0.56 (0.40, 0.73)	106 (p < 0.0001)
Active SPMS		-0.68	-0.02		347/169	0.67 (0.52, 0.82)	99 (<i>p</i> < 0.0001)
Without superimposed relapses	s	-0.56		0.03	431/205	0.59 (0.45, 0.74)	105 (p < 0.0001)
With superimposed relapses		-0.68	-0.03		259/131	0.65 (0.47, 0.83)	96 (<i>p</i> < 0.0001)
Without Gd+ lesions		-0.56		0.04	530/268	0.60 (0.47, 0.73)	107 (p < 0.0001)
With Gd+ lesions		-0.75	-0.11		162/69	0.63 (0.41, 0.86)	84 (<i>p</i> < 0.0001)
	-1.40 -1	.00 –0.60	0 –0.20	0.20		Subgroups by disease Subgroups by inflamm	history and severity atory disease activi
(b)	–1.40 –1 Percen	.00 –0.60 tage change i from baseline	n cGM volume to M12	0.20	n/n (sinonimod/	Subgroups by disease Subgroups by inflamm Between-treatment	history and severity atory disease activit Percentage
(b) Subgroups	–1.40 –1 Percen	.00 –0.60 htage change i from baseline ■ Placebo	 –0.20 n cGM volume to M12 Siponimod 	0.20	n/n (siponimod/ placebo)	Subgroups by disease Subgroups by inflamm Between-treatment difference (95% CI)	history and severity atory disease activit Percentage reduction vs placebo (p value)
(b) Subgroups Age ≤ 45 years	–1.40 –1 Percen	00 −0.60 tage change i from baseline Placebo	 -0.20 n cGM volume to M12 Siponimod -0.30 	0.20	n/n (siponimod/ placebo) 246/120	Subgroups by disease Subgroups by inflamm Between-treatment difference (95% Cl) 0.65 (0.36, 0.93)	history and severity atory disease activit Percentage reduction vs placebo (p value 69 (p < 0.0001)
(b) Subgroups Age ≤ 45 years Age > 45 years	-1.40 -1 Percen -0.5	00 −0.60 tage change i from baseline Placebo 04 −0.4	 –0.20 n cGM volume to M12 Siponimod –0.30 5 	0.20	<i>n/n</i> (siponimod/ placebo) 246/120 446/217	Subgroups by disease Subgroups by inflamm Between-treatment difference (95% Cl) 0.65 (0.36, 0.93) 0.62 (0.41, 0.83)	history and severity atory disease activit Percentage reduction vs placebo (<i>p</i> value 69 (<i>p</i> < 0.0001) 57 (<i>p</i> < 0.0001)
(b) Subgroups Age ≤ 45 years Age > 45 years Disease duration ≤ 15 years	-1.40 -1 Percen -0.5 -1.08	0.00 −0.60 tage change i from baseline Placebo) -0.20 n cGM volume to M12 Siponimod -0.30 5 5	0.20	n/n (siponimod/ placebo) 246/120 446/217 318/171	Subgroups by disease Subgroups by inflamm Between-treatment difference (95% Cl) 0.65 (0.36, 0.93) 0.62 (0.41, 0.83) 0.69 (0.45, 0.94)	history and severity atory disease activit Percentage reduction vs placebo (<i>p</i> value) 69 (<i>p</i> < 0.0001) 57 (<i>p</i> < 0.0001) 66 (<i>p</i> < 0.0001)
(b) Subgroups Age ≤ 45 years Age > 45 years Disease duration ≤ 15 years Disease duration > 15 years	-1.40 -1 Percen -0.5 -1.08 -1.05 -1.04	0.00 −0.6C tage change i from baseline Placebo 94 −0.4 −0.4) -0.20 n cGM volume to M12 -0.30 5 0.36 42	0.20	n/n (siponimod/ placebo) 246/120 446/217 318/171 374/165	Subgroups by disease Subgroups by inflamm Between-treatment difference (95% Cl) 0.65 (0.36, 0.93) 0.62 (0.41, 0.83) 0.69 (0.45, 0.94) 0.62 (0.39, 0.86)	history and severity atory disease activit Percentage reduction vs placebo (<i>p</i> value) 69 (<i>p</i> < 0.0001) 57 (<i>p</i> < 0.0001) 66 (<i>p</i> < 0.0001) 60 (<i>p</i> < 0.0001)
(b) Subgroups Age ≤ 45 years Age > 45 years Disease duration ≤ 15 years Disease duration > 15 years EDSS < 6.0	-1.40 -1 Percen -0.9 -1.08 -1.08 -1.04 -1.04	0.00 −0.66 tage change in from baseline Placebo 94 −0.4 −0.4) -0.20 n cGM volume to M12 -0.30 5 0.36 42 0.37	0.20	n/n (siponimod/ placebo) 246/120 446/217 318/171 374/165 319/165	Subgroups by disease Subgroups by inflamm Between-treatment difference (95% Cl) 0.65 (0.36, 0.93) 0.62 (0.41, 0.83) 0.69 (0.45, 0.94) 0.62 (0.39, 0.86) 0.67 (0.45, 0.90)	history and severity atory disease activit Percentage reduction vs placebo (p value) 69 (p < 0.0001) 57 (p < 0.0001) 66 (p < 0.0001) 60 (p < 0.0001) 64 (p < 0.0001)
(b) Subgroups Age ≤ 45 years Age > 45 years Disease duration ≤ 15 years Disease duration > 15 years EDSS < 6.0 EDSS ≥ 6.0	-1.40 -1 Percen	00 -0.66 tage change i from baseline Placebo 24 -0.4 -0.4 -0.4) -0.20 n cGM volume to M12 -0.30 5 0.36 42 0.37	0.20	n/n (siponimod/ placebo) 246/120 446/217 318/171 374/165 319/165 373/172	Subgroups by disease Subgroups by inflamm difference (95% Cl) 0.65 (0.36, 0.93) 0.62 (0.41, 0.83) 0.69 (0.45, 0.94) 0.62 (0.39, 0.86) 0.67 (0.45, 0.90) 0.62 (0.37, 0.88)	history and severity atory disease activit Percentage reduction vs placebo (p value) 69 (p < 0.0001) 57 (p < 0.0001) 66 (p < 0.0001) 60 (p < 0.0001) 60 (p < 0.0001)
(b) Subgroups Age ≤ 45 years Age > 45 years Disease duration ≤ 15 years Disease duration > 15 years EDSS < 6.0 EDSS ≥ 6.0 SDMT > 43	-1.40 -1 Percen -0.6 -1.08 -1.08 -1.04 -1.04 -1.04 -0.98	00 -0.66 tage change i from baseline Placebo 24 -0.4 -0.4 -0.) -0.20 n cGM volume to M12 Siponimod -0.30 5 0.36 42 0.37 42 -0.23	0.20	n/n (siponimod/ placebo) 246/120 446/217 318/171 318/171 374/165 319/165 3319/165 373/172 299/159	Subgroups by disease Subgroups by inflamm difference (95% Cl) 0.65 (0.36, 0.93) 0.62 (0.41, 0.83) 0.69 (0.45, 0.94) 0.62 (0.39, 0.86) 0.67 (0.45, 0.90) 0.62 (0.37, 0.88) 0.74 (0.49, 0.99)	history and severity atory disease activit Percentage reduction vs placebo (p value 69 (p < 0.0001) 57 (p < 0.0001) 66 (p < 0.0001) 60 (p < 0.0001) 64 (p < 0.0001) 60 (p < 0.0001) 76 (p < 0.0001)
b) Subgroups Age \leq 45 years Age $>$ 45 years Disease duration \leq 15 years Disease duration $>$ 15 years EDSS $<$ 6.0 EDSS \geq 6.0 EDSS \geq 6.0 SDMT $>$ 43 SDMT \leq 43	-1.40 -1 Percen -0.8 -1.08 -1.08 -1.04 -1.04 -1.04 -0.98 -1.11	0.00 -0.60 tage change i from baseline ■ Placebo 94 -0.4 -0. -0. -0.51) -0.20 n cGM volume to M12 Siponimod -0.30 5 0.36 42 0.37 42 -0.23	0.20	n/n (siponimod/ placebo) 246/120 446/217 318/171 374/165 319/165 373/172 299/159 387/176	Subgroups by disease Subgroups by inflamm difference (95% Cl) 0.65 (0.36, 0.93) 0.62 (0.41, 0.83) 0.69 (0.45, 0.94) 0.62 (0.39, 0.86) 0.67 (0.45, 0.90) 0.62 (0.37, 0.88) 0.74 (0.49, 0.99) 0.60 (0.37, 0.84)	history and severity atory disease activi Percentage reduction vs placebo (<i>p</i> value 69 (<i>p</i> < 0.0001) 57 (<i>p</i> < 0.0001) 66 (<i>p</i> < 0.0001) 60 (<i>p</i> < 0.0001) 60 (<i>p</i> < 0.0001) 76 (<i>p</i> < 0.0001) 54 (<i>p</i> < 0.0001)
(b) Subgroups Age ≤ 45 years Age > 45 years Disease duration ≤ 15 years Disease duration > 15 years EDSS < 6.0 EDSS ≥ 6.0 SDMT > 43 SDMT ≤ 43 Non-active SPMS	-1.40 -1 Percen Percen -1.08 -1.04 -1.04 -0.98 -1.11	00 -0.66 trage change i from baseline Placebo 24 -0.4 -0.51) -0.20 n cGM volume to M12 Siponimod -0.30 5 0.36 42 -0.23 -0.27	0.20	n/n (siponimod/ placebo) 246/120 446/217 318/171 318/171 374/165 319/165 339/159 387/176 387/176	Subgroups by disease Subgroups by inflamm difference (95% Cl) 0.65 (0.36, 0.93) 0.62 (0.41, 0.83) 0.69 (0.45, 0.94) 0.62 (0.39, 0.86) 0.67 (0.45, 0.90) 0.62 (0.37, 0.88) 0.74 (0.49, 0.99) 0.60 (0.37, 0.84) 0.68 (0.43, 0.92)	history and severity atory disease activi Percentage reduction vs placebo (p value 69 ($p < 0.0001$) 57 ($p < 0.0001$) 66 ($p < 0.0001$) 60 ($p < 0.0001$) 64 ($p < 0.0001$) 60 ($p < 0.0001$) 76 ($p < 0.0001$) 74 ($p < 0.0001$) 72 ($p < 0.0001$)
(b) Subgroups Age ≤ 45 years Age > 45 years Disease duration ≤ 15 years Disease duration > 15 years EDSS < 6.0 EDSS > 6.0 EDSS > 6.0 SDMT > 43 SDMT ≤ 43 Non-active SPMS Active SPMS	-1.40 -1 Percen Percen -1.08 -1.04 -1.04 -0.98 -1.11 -0.98 -1.11	00 -0.66 tage change i from baseline Placebo 4 -0.4 -0.51 -0.51) -0.20 n cGM volume to M12 Siponimod 51 0.36 42 -0.23 -0.23	0.20	n/n (siponimod/ placebo) 246/120 446/217 318/171 374/165 319/165 319/165 3319/165 339/159 387/176	Subgroups by disease Subgroups by inflamm difference (95% Cl) 0.65 (0.36, 0.93) 0.62 (0.41, 0.83) 0.69 (0.45, 0.94) 0.62 (0.39, 0.86) 0.67 (0.45, 0.90) 0.62 (0.37, 0.88) 0.74 (0.49, 0.99) 0.60 (0.37, 0.84) 0.68 (0.43, 0.92) 0.63 (0.40, 0.86)	history and severity atory disease activit Percentage reduction vs placebo (p value 69 ($p < 0.0001$) 57 ($p < 0.0001$) 66 ($p < 0.0001$) 60 ($p < 0.0001$) 60 ($p < 0.0001$) 76 ($p < 0.0001$) 76 ($p < 0.0001$) 54 ($p < 0.0001$) 72 ($p < 0.0001$) 55 ($p < 0.0001$)
(b) Subgroups Age ≤ 45 years Age > 45 years Disease duration ≤ 15 years Disease duration > 15 years EDSS < 6.0	-1.40 -1 Percen Percen -1.08 -1.04 -1.04 -1.04 -0.98 -1.11 -0.98 -1.11 -0.98 -1.11 -0.98 -1.11 -0.98 -1.11 -0.98 -1.11	00 -0.60 tage change i from baseline Placebo -0.4 -0.4 -0.51 -0.51 -0.51) -0.20 n cGM volume to M12 Siponimod 0.30 5 0.36 42 -0.23 -0.23 -0.23	0.20	n/n (siponimod/ placebo) 246/120 446/217 318/171 374/165 319/165 319/165 3319/165 339/172 299/159 387/176 344/167 344/169 431/205	Subgroups by disease Subgroups by inflamm difference (95% Cl) 0.65 (0.36, 0.93) 0.62 (0.41, 0.83) 0.69 (0.45, 0.94) 0.62 (0.39, 0.86) 0.67 (0.45, 0.90) 0.62 (0.37, 0.88) 0.74 (0.49, 0.99) 0.60 (0.37, 0.84) 0.68 (0.43, 0.92) 0.63 (0.40, 0.86) 0.66 (0.44, 0.89)	history and severity atory disease activit Percentage reduction vs placebo (p value 69 ($p < 0.0001$) 57 ($p < 0.0001$) 66 ($p < 0.0001$) 60 ($p < 0.0001$) 60 ($p < 0.0001$) 76 ($p < 0.0001$) 76 ($p < 0.0001$) 72 ($p < 0.0001$) 55 ($p < 0.0001$) 70 ($p < 0.0001$)
(b) Subgroups Age ≤ 45 years Age > 45 years Disease duration ≤ 15 years Disease duration > 15 years EDSS < 6.0 EDSS ≥ 6.0 SDMT > 43 SDMT ≤ 43 Non-active SPMS Active SPMS Without superimposed relapses With superimposed relapses	-1.40 -1 Percen Percen -1.08 -1.04 -1.04 -1.04 -0.98 -1.11 -0.98 -1.11 -0.98 -1.11 s -0.9 s -0.98	00 -0.60 tage change in from baseline Placebo -0.4 -0.4 -0.51 -0.51 -0.51 -0.51) -0.20 n cGM volume to M12 Siponimod -0.30 5 0.36 42 -0.23 -0.23 -0.23	0.20	n/n (siponimod/ placebo) 246/120 446/217 318/171 374/165 319/165 319/165 3319/175 3419/175 3319/175 3419/175 3419/175 34	Subgroups by disease Subgroups by inflamm difference (95% Cl) 0.65 (0.36, 0.93) 0.62 (0.41, 0.83) 0.69 (0.45, 0.94) 0.62 (0.39, 0.86) 0.67 (0.45, 0.90) 0.62 (0.37, 0.88) 0.74 (0.49, 0.99) 0.60 (0.37, 0.84) 0.68 (0.43, 0.92) 0.63 (0.40, 0.86) 0.66 (0.44, 0.89) 0.60 (0.34, 0.85)	history and severity atory disease activit Percentage reduction vs placebo (p value 69 ($p < 0.0001$) 57 ($p < 0.0001$) 66 ($p < 0.0001$) 60 ($p < 0.0001$) 60 ($p < 0.0001$) 76 ($p < 0.0001$) 76 ($p < 0.0001$) 72 ($p < 0.0001$) 55 ($p < 0.0001$) 70 ($p < 0.0001$) 51 ($p < 0.0001$)
(b) Subgroups Age ≤ 45 years Age > 45 years Disease duration ≤ 15 years Disease duration > 15 years EDSS < 6.0 EDSS ≥ 6.0 SDMT > 43 SDMT ≤ 43 Non-active SPMS Active SPMS Without superimposed relapses Without Gd+ lesions	-1.40 -1 Percen Percen -1.08 -1.08 -1.04 -0.98 -1.11 -0.98 -1.11 -0.98 -1.11 -0.98 -1.11 -0.98 -1.11	00 -0.60 tage change i from baseline Placebo Placebo -0.4 -0.4 -0.51 94 -0.51 94 -0.50)0.20 n cGM volume to M12 Siponimod -0.30 5 0.36 42 -0.23 -0.23 -0.23 -0.28 0.34	0.20	n/n (siponimod/ placebo) 246/120 446/217 318/171 374/165 319/165 319/165 3319/165 3319/165 3319/165 3319/165 3319/165 3319/165 3319/165 3341/167 344/167 344/167 344/167 343/1205 259/131 530/268	Subgroups by disease Subgroups by inflamm Between-treatment difference (95% Cl) 0.65 (0.36, 0.93) 0.62 (0.41, 0.83) 0.69 (0.45, 0.94) 0.62 (0.39, 0.86) 0.67 (0.45, 0.90) 0.62 (0.37, 0.88) 0.74 (0.49, 0.99) 0.60 (0.37, 0.84) 0.68 (0.43, 0.92) 0.63 (0.40, 0.86) 0.66 (0.44, 0.89) 0.60 (0.34, 0.85) 0.67 (0.48, 0.86)	history and severity atory disease activit Percentage reduction vs placebo (p value 69 ($p < 0.0001$) 57 ($p < 0.0001$) 66 ($p < 0.0001$) 60 ($p < 0.0001$) 60 ($p < 0.0001$) 76 ($p < 0.0001$) 76 ($p < 0.0001$) 72 ($p < 0.0001$) 55 ($p < 0.0001$) 70 ($p < 0.0001$) 71 ($p < 0.0001$) 56 ($p < 0.0001$) 66 ($p < 0.0001$)
(b) Subgroups Age ≤ 45 years Age > 45 years Disease duration ≤ 15 years Disease duration > 15 years EDSS < 6.0 EDSS > 6.0 EDSS > 6.0 SDMT > 43 SDMT ≤ 43 Non-active SPMS Active SPMS Without superimposed relapses Without Gd+ lesions With Gd+ lesions	-1.40 -1 Percen Percen -1.08 -1.08 -1.04 -0.98 -1.11 -0.98 -1.11 -0.98 -1.11 -0.98 -1.11 -0.98 -1.11 -0.98 -1.11	00 -0.60 tage change i from baseline Placebo Placebo -0.4 -0.4 -0.4 -0.4 -0.4 -0.4 -0.4 -0.4 -0.4 -0.4 -0.4 -0.4 -0.4 -0.4 -0.51 -0.51 -0.51 -0.51 -0.51 -0.51 -0.51 -0.51 -0.51 -0.51 -0.51 -0.51 -0.51 -0.51 -0.55) -0.20 n cGM volume to M12 Siponimod -0.30 5 0.36 42 -0.23 -0.23 -0.23 0.34	0.20	n/n (siponimod/ placebo) 246/120 446/217 318/171 374/165 319/165 3	Subgroups by disease Subgroups by inflamm Between-treatment difference (95% Cl) 0.65 (0.36, 0.93) 0.65 (0.36, 0.93) 0.62 (0.41, 0.83) 0.69 (0.45, 0.94) 0.62 (0.39, 0.86) 0.67 (0.45, 0.90) 0.62 (0.37, 0.88) 0.74 (0.49, 0.99) 0.60 (0.37, 0.84) 0.68 (0.43, 0.92) 0.63 (0.40, 0.86) 0.66 (0.44, 0.89) 0.60 (0.34, 0.85) 0.67 (0.48, 0.86) 0.53 (0.14, 0.93)	history and severity atory disease activi Percentage reduction vs placebo (p value 69 ($p < 0.0001$) 57 ($p < 0.0001$) 66 ($p < 0.0001$) 60 ($p < 0.0001$) 60 ($p < 0.0001$) 60 ($p < 0.0001$) 76 ($p < 0.0001$) 76 ($p < 0.0001$) 72 ($p < 0.0001$) 55 ($p < 0.0001$) 70 ($p < 0.0001$) 71 ($p < 0.0001$) 51 ($p < 0.0001$

Figure 2. Percentage change in cGM volume (a) from baseline to month 12 and (b) from baseline to month 24 by subgroups according to baseline age, disease duration, severity, or activity^a in the combined MRI cohort (PPS^b). cGM: cortical gray matter; CI: confidence interval; EDSS: Expanded Disability Status Scale; FAS, full analysis set; Gd+: gadolinium-enhancing; M: month; MRI: magnetic resonance imaging; PPS: per-protocol set; SDMT: Symbol Digit Modalities Test; SPMS: secondary progressive multiple sclerosis.

^aPatients were considered to have active SPMS if they had ≥1 relapse in the 2 years before the study and/or had ≥1 Gd+ lesion at baseline; superimposed relapses and Gd+ lesions subgroups are based on events 2 years before or at baseline, respectively. ^bPPS included all patients from the FAS who did not have any major protocol deviations that could confound interpretation.

Discussion

MRI measures of GM atrophy and brain tissue integrity/myelination provide important insights into changes occurring in brain tissue and may be seen as indicators of chronic, compartmentalized CNS inflammation and neurodegeneration, the primary drivers of progression in patients with SPMS.³⁰ Treatment response on these MRI markers may

(a) Subgroups		Pla	acebo	Siponimod	(siponimod/ placebo)	difference (95% CI)	reduction vs placebo (p value)
Age ≤ 45 years				-1.16	247/121	0.77 (0.41, 1.14)	66 (<i>p</i> < 0.0001)
Age > 45 years				-0.82	449/221	0.30 (0.06, 0.54)	37 (p = 0.0159)
Disease duration ≤ 15 years				-1.20	320/173	0.71 (0.40, 1.02)	59 (<i>p</i> < 0.0001)
Disease duration > 15 years				-0.67	376/168	0.22 (-0.04, 0.48)	33 (p = 0.1029)
EDSS < 6.0				-0.98	320/169	0.58 (0.29, 0.87)	59 (<i>p</i> < 0.0001)
EDSS ≥ 6.0				-0.90	376/173	0.37 (0.08, 0.65)	41 (p = 0.0112)
SDMT > 43				-0.77	301/158	0.48 (0.19, 0.77)	62 (p = 0.0013)
SDMT ≤ 43				-1.08	389/181	0.48 (0.19, 0.77)	44 (<i>p</i> = 0.0011)
Non-active SPMS				-0.63	347/168	0.43 (0.15, 0.72)	68 (p = 0.0028)
Active SPMS				-1.24	348/173	0.50 (0.21, 0.79)	40 (p = 0.0008)
Without superimposed relapse	s			-0.82	436/210	0.44 (0.19, 0.70)	54 (p = 0.0007)
With superimposed relapses				-1.17	258/131	0.56 (0.22, 0.89)	48 (p = 0.0012)
Without Gd+ lesions				-0.68	532/269	0.41 (0.19, 0.64)	60 (p = 0.0003)
With Gd+ lesions			-1.78	-1.19	164/73	0.59 (0.12, 1.06)	33 (p = 0.0150)
	-4.00 Perc	-3.00 entage cha	-2.00 ange in t	-1.00	0	Subgroups by disease Subgroups by inflamma	atory disease activi
		from b	aseline	to M12			
(b) Subgroups		from b	aseline	 Siponimod 	<i>n n</i> (siponimod/ placebo)	Between-treatment difference (95% CI)	Percentage reduction vs placebo (<i>p</i> value
(b) Subgroups Age ≤ 45 years		from b	acebo	 Siponimod 	n/n (siponimod/ placebo) 247/121	Between-treatment difference (95% CI) 1.30 (0.68, 1.92)	Percentage reduction vs placebo (<i>p</i> value 61 (<i>p</i> < 0.0001)
(b) Subgroups Age ≤ 45 years Age > 45 years		from b ■ Pla -2	acebo	 Siponimod -0.82 -112 	n/n (siponimod/ placebo) 247/121 449/221	Between-treatment difference (95% Cl) 1.30 (0.68, 1.92) 0.51 (0.11, 0.91)	Percentage reduction vs placebo (p value 61 (p < 0.0001) 31 (p = 0.0136)
(b) Subgroups Age ≤ 45 years Age > 45 years Disease duration ≤ 15 years		from b ■ Pla -2	acebo 12 2.09	 Siponimod -0.82 -1.12 -1.18 	n/n (siponimod/ placebo) 247/121 449/221 320/173	Between-treatment difference (95% Cl) 1.30 (0.68, 1.92) 0.51 (0.11, 0.91) 0.91 (0.42, 1.40)	Percentage reduction vs placebo (p value 61 (p < 0.0001) 31 (p = 0.0136) 44 (p = 0.0003)
(b) Subgroups Age < 45 years Age > 45 years Disease duration < 15 years Disease duration > 15 years		from b ■ Pla -2	acebo 12 	Siponimod -0.82 -1.12 -1.18 -0.85	n/n (siponimod/ placebo) 247/121 449/221 320/173 376/168	Between-treatment difference (95% Cl) 1.30 (0.68, 1.92) 0.51 (0.11, 0.91) 0.91 (0.42, 1.40) 0.59 (0.13, 1.06)	Percentage reduction vs placebo (p value 61 (p < 0.0001) 31 (p = 0.0136) 44 (p = 0.0003) 41 (p = 0.0120)
(b) Subgroups Age < 45 years Age > 45 years Disease duration < 15 years Disease duration > 15 years EDSS < 6.0		from b ■ Pla -2	acebo 	Siponimod -0.82 -1.12 -1.18 -0.85 -0.85 -0.98	n/n (siponimod/ placebo) 247/121 449/221 320/173 376/168 320/169	Between-treatment difference (95% Cl) 1.30 (0.68, 1.92) 0.51 (0.11, 0.91) 0.91 (0.42, 1.40) 0.59 (0.13, 1.06) 0.73 (0.27, 1.19)	Percentage reduction vs placebo (p value 61 (p < 0.0001) 31 (p = 0.0136) 44 (p = 0.0003) 41 (p = 0.0120) 43 (p = 0.0021)
(b) Subgroups Age < 45 years Age > 45 years Disease duration < 15 years Disease duration > 15 years EDSS < 6.0 EDSS > 6.0		from b	acebo .12 	Siponimod -0.82 -0.82 -1.12 -1.18 -0.98 -0.98 -0.98	n/n (siponimod/ placebo) 247/121 449/221 320/173 376/168 320/169 376/173	Between-treatment difference (95% Cl) 1.30 (0.68, 1.92) 0.51 (0.11, 0.91) 0.91 (0.42, 1.40) 0.59 (0.13, 1.06) 0.73 (0.27, 1.19) 0.88 (0.39, 1.37)	Percentage reduction vs placebo (p value 61 ($p < 0.0001$) 31 ($p = 0.0136$) 44 ($p = 0.0003$) 41 ($p = 0.0120$) 43 ($p = 0.0021$) 47 ($p = 0.0005$)
(b) Subgroups Age \leq 45 years Age $>$ 45 years Disease duration \leq 15 years Disease duration $>$ 15 years EDSS $<$ 6.0 EDSS \geq 6.0 SDMT $>$ 43		from b ■ Pla -2	acebo 	Siponimod -0.82 -0.82 -1.12 -1.18 -0.98 -0.98 -1.00 54 -0.81	n/n (siponimod/ placebo) 247/121 449/221 320/173 376/168 320/169 376/173 301/158	Between-treatment difference (95% Cl) 1.30 (0.68, 1.92) 0.51 (0.11, 0.91) 0.91 (0.42, 1.40) 0.59 (0.13, 1.06) 0.73 (0.27, 1.19) 0.88 (0.39, 1.37) 0.72 (0.24, 1.21)	Percentage reduction vs placebo (p value 61 ($p < 0.0001$) 31 ($p = 0.0136$) 44 ($p = 0.0003$) 41 ($p = 0.0120$) 43 ($p = 0.0021$) 47 ($p = 0.0005$) 47 ($p = 0.0034$)
b) Subgroups Age \leq 45 years Age $>$ 45 years Disease duration \leq 15 years Disease duration $>$ 15 years EDSS $<$ 6.0 EDSS \geq 6.0 SDMT $>$ 43 SDMT \leq 43		from b	acebo 	Siponimod -0.82 -1.12 -1.18 -0.98 -0.98 -0.98 -1.00 54 -0.81 -1.16	n/n (siponimod/ placebo) 247/121 449/221 320/173 376/168 320/169 376/173 301/158 389/181	Between-treatment difference (95% Cl) 1.30 (0.68, 1.92) 0.51 (0.11, 0.91) 0.91 (0.42, 1.40) 0.59 (0.13, 1.06) 0.73 (0.27, 1.19) 0.88 (0.39, 1.37) 0.72 (0.24, 1.21) 0.83 (0.35, 1.30)	Percentage reduction vs placebo (p value 61 ($p < 0.0001$) 31 ($p = 0.0136$) 44 ($p = 0.0003$) 41 ($p = 0.0120$) 43 ($p = 0.0021$) 47 ($p = 0.0005$) 47 ($p = 0.0005$) 47 ($p = 0.0003$)
(b) Subgroups Age ≤ 45 years Age > 45 years Disease duration ≤ 15 years Disease duration > 15 years EDSS < 6.0 EDSS ≥ 6.0 SDMT > 43 SDMT ≤ 43 Non-active SPMS		from b	acebo 12 2.09 	Lo M12	n/n (siponimod/ placebo) 247/121 449/221 320/173 376/168 320/169 376/173 301/158 389/181	Between-treatment difference (95% Cl) 1.30 (0.68, 1.92) 0.51 (0.11, 0.91) 0.91 (0.42, 1.40) 0.59 (0.13, 1.06) 0.73 (0.27, 1.19) 0.88 (0.39, 1.37) 0.72 (0.24, 1.21) 0.83 (0.35, 1.30) 0.78 (0.32, 1.23)	Percentage reduction vs placebo (p value 61 (p < 0.0001) 31 (p = 0.0136) 44 (p = 0.003) 41 (p = 0.0120) 43 (p = 0.0021) 47 (p = 0.0005) 47 (p = 0.0005) 42 (p = 0.0007) 58 (p = 0.0009)
(b) Subgroups Age ≤ 45 years Age > 45 years Disease duration ≤ 15 years Disease duration > 15 years EDSS < 6.0 EDSS ≥ 6.0 SDMT > 43 SDMT ≤ 43 Non-active SPMS Active SPMS		from b ■ Pla -2 -2	-1.60 -1.71 -1.88 -1.71 -1.88 -1. -1.99	Lo M12	n/n (siponimod/ placebo) 247/121 449/221 320/173 376/168 320/169 376/173 301/158 389/181 347/168 348/173	Between-treatment difference (95% Cl) 1.30 (0.68, 1.92) 0.51 (0.11, 0.91) 0.91 (0.42, 1.40) 0.59 (0.13, 1.06) 0.73 (0.27, 1.19) 0.88 (0.39, 1.37) 0.72 (0.24, 1.21) 0.83 (0.35, 1.30) 0.78 (0.32, 1.23) 0.73 (0.25, 1.22)	Percentage reduction vs placebo (p value 61 ($p < 0.0001$) 31 ($p = 0.0136$) 44 ($p = 0.0003$) 41 ($p = 0.0120$) 43 ($p = 0.0021$) 47 ($p = 0.0005$) 47 ($p = 0.0034$) 42 ($p = 0.0007$) 58 ($p = 0.0009$) 34 ($p = 0.0032$)
(b) Subgroups Age < 45 years	S	from b ■ Pla -2 -2 -2	acebo 	Lo M12	n/n (siponimod/ placebo) 247/121 449/221 320/173 376/168 320/169 376/173 301/158 389/181 347/168 348/173 436/210	Between-treatment difference (95% Cl) 1.30 (0.68, 1.92) 0.51 (0.11, 0.91) 0.91 (0.42, 1.40) 0.59 (0.13, 1.06) 0.73 (0.27, 1.19) 0.88 (0.39, 1.37) 0.72 (0.24, 1.21) 0.83 (0.35, 1.30) 0.78 (0.32, 1.23) 0.73 (0.25, 1.22) 0.98 (0.54, 1.43)	Percentage reduction vs placebo (p value 61 ($p < 0.0001$) 31 ($p = 0.0136$) 44 ($p = 0.0003$) 41 ($p = 0.0120$) 43 ($p = 0.0021$) 47 ($p = 0.0005$) 48 ($p = 0.0005$) 49 ($p = 0.0005$) 49 ($p = 0.0005$) 40 ($p = 0.0005$) 58 ($p = 0.0009$) 34 ($p = 0.0032$) 54 ($p < 0.0001$)
(b) Subgroups Age < 45 years Age > 45 years Disease duration < 15 years Disease duration > 15 years EDSS < 6.0 EDSS > 6.0 SDMT > 43 SDMT < 43 Non-active SPMS Active SPMS Without superimposed relapse With superimposed relapses	S	from b ■ Pla -2 -2 -2	acebo .12	Lo M12	n/n (siponimod/ placebo) 247/121 449/221 320/173 376/168 320/169 376/173 301/158 389/181 3389/181 347/168 348/173 436/210 258/131	Between-treatment difference (95% Cl) 1.30 (0.68, 1.92) 0.51 (0.11, 0.91) 0.91 (0.42, 1.40) 0.59 (0.13, 1.06) 0.73 (0.27, 1.19) 0.88 (0.39, 1.37) 0.72 (0.24, 1.21) 0.83 (0.35, 1.30) 0.78 (0.32, 1.23) 0.73 (0.25, 1.22) 0.98 (0.54, 1.43) 0.54 (0.02, 1.06)	Percentage reduction vs placebo (p value 61 ($p < 0.0001$) 31 ($p = 0.0136$) 44 ($p = 0.0003$) 41 ($p = 0.0120$) 43 ($p = 0.0021$) 47 ($p = 0.0005$) 58 ($p = 0.0005$) 58 ($p = 0.0005$) 34 ($p = 0.0032$) 54 ($p < 0.0001$) 30 ($p = 0.0415$)
(b) Subgroups Age \leq 45 years Age \geq 45 years Disease duration \leq 15 years Disease duration \geq 15 years EDSS \leq 6.0 EDSS \geq 6.0 SDMT \geq 43 SDMT \leq 43 Non-active SPMS Active SPMS Without superimposed relapses Without Gd+ lesions	s	from b ■ Pla -2 -2	acebo 12 -1.6: 2.09 -1 -1.71 -1.88 -1. -1.99 -1. -1.99 -1.82 -1. -1.82 -1.	Lo M12 Siponimod -0.82 -1.12 -1.18 -1.18 -0.98 -1.00 54 -0.98 -1.00 54 -0.81 -1.16 -1.16 -1.16 -1.28 -1.	n/n (siponimod/ placebo) 247/121 449/221 320/173 376/168 320/169 376/173 301/158 389/181 389/181 347/168 348/173 436/210 258/131	Between-treatment difference (95% Cl) 1.30 (0.68, 1.92) 0.51 (0.11, 0.91) 0.91 (0.42, 1.40) 0.59 (0.13, 1.06) 0.73 (0.27, 1.19) 0.88 (0.39, 1.37) 0.72 (0.24, 1.21) 0.83 (0.35, 1.30) 0.78 (0.32, 1.23) 0.73 (0.25, 1.22) 0.98 (0.54, 1.43) 0.54 (0.02, 1.06) 0.64 (0.28, 0.99)	Percentage reduction vs placebo (p value 61 ($p < 0.0001$) 31 ($p = 0.0136$) 44 ($p = 0.0003$) 41 ($p = 0.0120$) 43 ($p = 0.0021$) 47 ($p = 0.0005$) 47 ($p = 0.0034$) 42 ($p = 0.0007$) 58 ($p = 0.0009$) 34 ($p = 0.0032$) 54 ($p < 0.0001$) 30 ($p = 0.0415$) 49 ($p = 0.0005$)
b) Subgroups Age < 45 years Age > 45 years Disease duration < 15 years Disease duration > 15 years EDSS < 6.0 EDSS < 6.0 EDSS > 6.0 SDMT > 43 SDMT < 43 Non-active SPMS Active SPMS Without superimposed relapses Without G4+ lesions With G4+ lesions	S -3.56	from b ■ Pla -2 -2 -2 -2 -2 -2 -2 -	azeline acebo 1.12 -1.6: -1.71 -1.88 -1. -1.71 -1.88 -1. -1.80 -1.80 -1.80 -1.82 -1.80 -1.82	to M12 Siponimod -0.82 -1.12 -1.18 -0.98 -0.98 -1.00 54 -0.98 -1.00 54 -0.81 -1.16 -1.16 -1.34 -0.85 -1.12 -1.18 -1.12 -1.18 -0.85 -0.85 -0.98 -1.00 54 -0.85 -0.85 -0.98 -1.00 -1.12 -1.12 -1.12 -1.12 -0.85 -0.98 -1.00 -1.12 -1.12 -1.12 -1.12 -1.12 -0.85 -0.98 -1.00 -1.12 -1.16 -1.12 -1.16 -1.12 -1.16 -1.12 -1.16 -1.16 -1.16 -1.16 -1.16 -1.16 -1.16 -1.16 -1.16 -1.16 -1.16 -0.85 -1.10 -1.16 -1.16 -0.85 -1.10 -1.16 -1.16 -1.16 -0.85 -1.16 -0.85 -1.16 -1.16 -0.85 -1.10 -1.16 -1.16 -0.85 -1.16 -1.16 -1.16 -1.16 -1.16 -1.28 -1.28 -1.28 -1.28 -1.28 -1.28 -1.28 -1.28 -1.28 -0.67	n/n (siponimod/ placebo) 247/121 449/221 320/173 376/168 320/169 376/173 301/158 389/181 389/181 343/1768 348/173 436/210 258/131 532/269 164/73	Between-treatment difference (95% Cl) 1.30 (0.68, 1.92) 0.51 (0.11, 0.91) 0.91 (0.42, 1.40) 0.59 (0.13, 1.06) 0.73 (0.27, 1.19) 0.88 (0.39, 1.37) 0.72 (0.24, 1.21) 0.83 (0.35, 1.30) 0.78 (0.32, 1.23) 0.73 (0.25, 1.22) 0.98 (0.54, 1.43) 0.54 (0.02, 1.06) 0.64 (0.28, 0.99) 1.52 (0.73, 2.30)	Percentage reduction vs placebo (p value 61 ($p < 0.0001$) 31 ($p = 0.0136$) 44 ($p = 0.0120$) 43 ($p = 0.0021$) 47 ($p = 0.0005$) 47 ($p = 0.0005$) 47 ($p = 0.0005$) 47 ($p = 0.0007$) 58 ($p = 0.0007$) 58 ($p = 0.0007$) 54 ($p < 0.0001$) 30 ($p = 0.0415$) 49 ($p = 0.0005$) 43 ($p = 0.0002$)
(b) Subgroups Age ≤ 45 years Age > 45 years Disease duration ≤ 15 years Disease duration > 15 years EDSS < 6.0 EDSS ≥ 6.0 SDMT > 43 SDMT ≤ 43 Non-active SPMS Active SPMS Without superimposed relapses Without G4+ lesions With G4+ lesions	s -3.56 -4.00	from b ■ Pla -2 -2 -2 -2 -2 -2 -2 -2 -2 -2	acebo 112 -1.6: -1.7: -1.7: -1.88 -1. -1.88 -1. -1.99 -1.80 -1.80 -1. -1.80 -1.80 -1. -1.80 -1. -1.80 -1.80 -1. -1.80 -1. -1.80 -1. -1.80 -1. -1.80 -1. -1.80 -1. -1.80 -1. -1.80 -1. -1.80 -1. -1.80 -1. -1.80 -1. -1.80 -1. -1.80 -1. -1.80 -1. -1.80 -1. -1.80 -1. -1.80 -1. -1.80 -1. -1.80 -1. -2. -2.00 -1. -2.00 -1.80 -1. -2.00 -2.	to M12 Siponimod -0.82 -0.82 -1.12 -1.18 -0.98 -0.98 -1.00 54 -0.98 -1.00 54 -0.81 -1.16 -1.34 -0.56 -1.141 -0.62 -1.28 -1.28 -1.28 -1.28 -1.28 -1.00 -1.00	n/n (siponimod/ placebo) 247/121 320/173 376/168 320/169 376/173 301/158 389/181 389/181 347/168 348/173 436/210 258/131 532/269 164/73	Between-treatment difference (95% Cl) 1.30 (0.68, 1.92) 0.51 (0.11, 0.91) 0.91 (0.42, 1.40) 0.59 (0.13, 1.06) 0.73 (0.27, 1.19) 0.88 (0.39, 1.37) 0.72 (0.24, 1.21) 0.83 (0.35, 1.30) 0.78 (0.32, 1.23) 0.73 (0.25, 1.22) 0.98 (0.54, 1.43) 0.54 (0.02, 1.06) 0.64 (0.28, 0.99) 1.52 (0.73, 2.30) Subgroups by disease Subgroups by disease	Percentage reduction vs placebo (p value 61 ($p < 0.0001$) 31 ($p = 0.0136$) 44 ($p = 0.0120$) 43 ($p = 0.0021$) 47 ($p = 0.0005$) 47 ($p = 0.0005$) 47 ($p = 0.0005$) 47 ($p = 0.0007$) 58 ($p = 0.0009$) 34 ($p = 0.0002$) 54 ($p < 0.0001$) 30 ($p = 0.0415$) 49 ($p = 0.0005$) 43 ($p = 0.0002$) history and severit atory disease activ

Figure 3. Percentage change in thalamic volume (a) from baseline to month 12 and (b) from baseline to month 24 by subgroups according to baseline age, disease duration, severity, or activity^a in the combined standard-resolution and high-resolution MRI cohorts (PPS^b).

CI: confidence interval; EDSS: Expanded Disability Status Scale; FAS: full analysis set; Gd+: gadolinium-enhancing; M: month; PPS: per-protocol set; SDMT: Symbol Digit Modalities Test; SPMS: secondary progressive multiple sclerosis.

^aPatients were considered to have active SPMS if they had ≥ 1 relapse in the 2 years before the study and/or had ≥ 1 Gd+ lesion at baseline; superimposed relapses and Gd+ lesions subgroups are based on events 2 years before or at baseline, respectively. ^bPPS included all patients from the FAS who did not have any major protocol deviations that could confound interpretation.

therefore represent a therapeutic impact on these chronic inflammatory and neurodegenerative pathways. This analysis from EXPAND showed that, compared with placebo, siponimod is associated with slowing of both cortical and thalamic volume loss, improvement in brain tissue integrity/myelination



Figure 4. Change from baseline to months 12 and 24 in median nMTR^a in (a) NABT, (b) cGM, and (c) NAWM in the MTR subset (PPS^b).

cGM: cortical gray matter; CI: confidence interval; FAS: full analysis set; M: month; MTR: magnetization transfer ratio; NABT: normalappearing brain tissue; NAWM: normal-appearing white matter; nMTR: normalized magnetization transfer ratio; PPS: per-protocol set. ^aVariations in MTR acquired on different scanners were reduced by MTR normalization, by setting the MTR of high-confidence cGM to 0 and of high-confidence white matter to 1 on the MTR scan of a healthy control individual on the same scanner. ^bPPS included all patients from the FAS who did not have any major protocol deviations that could confound interpretation. (assessed by nMTR), and improvement in nMTR recovery in newly formed lesions in patients with SPMS. These findings are compatible with, although not proof of, a direct effect of siponimod on neurodegenerative processes beyond suppression of peripheral inflammation.

Siponimod consistently slowed the progression of cGM atrophy (by 46%-76%) and thalamic atrophy (by 30%-61%) across subgroups stratified by age,

disease duration, disease severity (both cognitive and physical), and inflammatory disease activity. A pronounced difference in the dynamics of volume loss was seen between cGM and the thalamus. The presence of gadolinium-enhancing lesions accelerated volume loss in the thalamus but had little impact on cGM atrophy. This observation suggests that different dynamics drive cGM atrophy (less affected by acute inflammatory activity) and thalamic atrophy (substantially affected by acute inflammatory activity).

(a) Subgroups		Pla	acebo	Sipo	nimod	<i>n/n</i> (siponimod/ placebo)	Between-treatment difference (95% Cl)	Percentage reduction vs placebo (p value
Age ≤ 45 years	-0.128				0.020	100/58	0.148 (0.057, 0.239)	116 (<i>p</i> = 0.002)
Age > 45 years			-0.0	30		175/98	0.024 (-0.019, 0.066)	77 (p = 0.272)
Disease duration ≤ 15 years		-0.064	4	0.019		131/84	0.045 (-0.007, 0.097)	70 (<i>p</i> = 0.090)
Disease duration > 15 years		-	-0.045	0.010	0.021	144/72	0.066 (0.005, 0.127)	147 (p = 0.035)
EDSS < 6.0		-0.0	59	-	0.002	133/78	0.061 (0.004, 0.117)	103 (<i>p</i> = 0.036)
EDSS ≥ 6.0			-0.043		0.006	142/78	0.049 (-0.012, 0.109)	114 (p = 0.111)
SDMT > 43		-0.064	4	-0.008		111/74	0.056 (-0.001, 0.113)	88 (<i>p</i> = 0.053)
SDMT ≤ 43			-0.044		0.008	159/82	0.051 (-0.003, 0.106)	118 (p = 0.064)
Non-active SPMS			-0.	027	0.019	129/71	0.046 (-0.022, 0.114)	170 (p = 0.183)
Active SPMS		-0.074	-	-0.006	0.010	146/85	0.068 (0.024, 0.113)	92 (p = 0.003)
Without superimposed relaps	ses		-0.03	33	0.013	163/81	0.046 (-0.012, 0.105)	139 (p = 0.121)
With superimposed relapses		-0.072		0.019		112/75	0.053 (0.003, 0.103)	74 (p = 0.040)
Without Gd+ lesions		-	-0.045		0.003	218/126	0.048 (0.002, 0.095)	107 (p = 0.043
With Gd+ lesions		-0.089	_	_	0.007	57/30	0.096 (0.029, 0.163)	108 (p = 0.006)
	Abso	ute change	e from I	oaseline	to M24 in		Subgroups by inflamma	alory disease activ
(b) Substance	Abso	lute change median	e from I nMTR	baseline I in NAB	to M24 in T	n/n (siponimod/	Between-treatment difference	Percentage reduction vs
(b) Subgroups	Abso	lute change median ■ Pla	e from I nMTR acebo	oaseline t in NAB ∎ Sipo	to M24 in T nimod	n/n (siponimod/ placebo)	Between-treatment difference (95% CI)	Percentage reduction vs placebo (p value
(b) Subgroups Age ≤ 45 years	Abso -0.134	lute change median ■ Pla	e from I nMTR acebo	oaseline t in NAB	to M24 in T nimod	n/n (siponimod/ placebo) 100/58	Between-treatment difference (95% Cl) 0.174 (0.071, 0.277)	Percentage reduction vs placebo (p value 129 ($p = 0.002$)
(b) Subgroups Age ≤ 45 years Age > 45 years	Abso -0.134	lute change median ■ Pla	e from I nMTR acebo	oaseline tin NAB [™] Sipo -0.017 -0.007	to M24 in T nimod	n/n (siponimod/ placebo) 100/58 175/98	Between-treatment difference (95% Cl) 0.174 (0.071, 0.277) 0.010 (-0.036, 0.056) 0.045 (-0.013, 0.103)	Percentage reduction vs placebo (<i>p</i> value 129 (<i>p</i> = 0.002) 59 (<i>p</i> = 0.665) 83 (<i>p</i> = 0.124)
(b) Subgroups Age ≤ 45 years Age > 45 years Disease duration ≤ 15 years	-0.134	lute change median I Pla	e from I nMTR acebo	oaseline a in NAB ■ Sipo -0.017 -0.007	to M24 in T nimod	n/n (siponimod/ placebo) 100/58 175/98 131/84	Between-treatment difference (95% Cl) 0.174 (0.071, 0.277) 0.010 (-0.036, 0.056) 0.045 (-0.013, 0.103) 0.0564 (-0.004, 0.131)	Percentage reduction vs placebo (<i>p</i> value 129 (<i>p</i> = 0.002) 59 (<i>p</i> = 0.665) 83 (<i>p</i> = 0.124)
(b) Subgroups Age ≤ 45 years Age > 45 years Disease duration ≤ 15 years Disease duration > 15 years EDSS ≤ 6.0	Abso	lute change median ■ Pla –0.0	e from I nMTR acebo 054 -0.038 0.048	0.017 -0.007 ■ -0.009	to M24 in T	n/n (siponimod/ placebo) a 100/58 175/98 131/84 144/72 133/78	Between-treatment difference (95% Cl) 0.174 (0.071, 0.277) 0.010 (-0.036, 0.056) 0.045 (-0.013, 0.103) 0.064 (-0.004, 0.131) 0.058 (-0.003, 0.110)	Percentage reduction vs placebo (p valu 129 (p = 0.002) 59 (p = 0.665) 83 (p = 0.124) 168 (p = 0.064) 121 (p = 0.064)
(b) Subgroups Age < 45 years Age > 45 years Disease duration < 15 years Disease duration > 15 years EDSS < 6.0 EDSS < 6.0	Abso -0.134	lute change median Pla -0.1	e from I nMTR acebo	oaseline t in NAB [™] Sipo -0.017 -0.007	to M24 in T	n/n (siponimod/ placebo) 100/58 175/98 131/84 144/72 133/78 142/78	Between-treatment difference (95% Cl) 0.174 (0.071, 0.277) 0.010 (-0.036, 0.056) 0.045 (-0.013, 0.103) 0.064 (-0.004, 0.131) 0.058 (-0.003, 0.119) 0.056 (-0.014, 0.132)	Percentage reduction vs placebo (<i>p</i> value 129 (<i>p</i> = 0.002) 59 (<i>p</i> = 0.665) 83 (<i>p</i> = 0.124) 168 (<i>p</i> = 0.064) 121 (<i>p</i> = 0.064) 144 (<i>p</i> = 0.116)
(b) Subgroups Age ≤ 45 years Age > 45 years Disease duration ≤ 15 years Disease duration > 15 years EDSS < 6.0 EDSS ≥ 6.0 SDMT > 43	Abso	lute change median ■ Pla -0.0	e from I nMTR acebo 054 -0.038 0.048 -0.039 58	oaseline t in NAB Sipo -0.017 -0.009	to M24 in T nimod 0.038 0.026 0.010	n/n (siponimod/ placebo) 100/58 175/98 131/84 131/84 144/72 133/78 142/78 111/74	Between-treatment difference (95% Cl) 0.174 (0.071, 0.277) 0.010 (-0.036, 0.056) 0.045 (-0.013, 0.103) 0.064 (-0.004, 0.131) 0.058 (-0.003, 0.119) 0.056 (-0.014, 0.126) 0.050 (-0.021, 0.120)	Percentage reduction vs placebo (p value 129 ($p = 0.002$) 59 ($p = 0.665$) 83 ($p = 0.124$) 168 ($p = 0.064$) 121 ($p = 0.064$) 144 ($p = 0.116$) 84 ($p = 0.161$)
(b) Subgroups Age ≤ 45 years Age > 45 years Disease duration ≤ 15 years Disease duration > 15 years EDSS < 6.0 EDSS ≥ 6.0 SDMT > 43 SDMT ≤ 43	Abso	lute change median Pla Pla -0.1	 from I nMTR acebo 054 -0.038 -0.039 58 -0.038 	-0.009	to M24 in T	n/n (siponimod/ placebo) 100/58 175/98 131/84 144/72 133/78 142/78 142/78 111/74 159/82	Between-treatment difference (95% Cl) 0.174 (0.071, 0.277) 0.010 (-0.036, 0.056) 0.045 (-0.013, 0.103) 0.064 (-0.004, 0.131) 0.058 (-0.003, 0.119) 0.056 (-0.014, 0.126) 0.050 (-0.021, 0.120) 0.056 (-0.001, 0.114)	Percentage reduction vs placebo (p value 59 ($p = 0.002$) 59 ($p = 0.665$) 83 ($p = 0.124$) 168 ($p = 0.064$) 121 ($p = 0.064$) 144 ($p = 0.116$) 84 ($p = 0.161$) 147 ($p = 0.055$)
(b) Subgroups Age \leq 45 years Age \geq 45 years Disease duration \leq 15 years Disease duration \geq 15 years EDSS \leq 6.0 EDSS \geq 6.0 SDMT \geq 43 SDMT \leq 43 Non-active SPMS	Abso	lute change median Pla	 from I nMTR acebo 054 -0.038 -0.039 58 -0.038 	-0.009	to M24 in nimod 0.032 0.010 0.017 0.018	n/n (siponimod/ placebo) 100/58 175/98 131/84 144/72 133/78 142/78 111/74 159/82	Between-treatment difference (95% Cl) 0.174 (0.071, 0.277) 0.010 (-0.036, 0.056) 0.045 (-0.013, 0.103) 0.064 (-0.004, 0.131) 0.058 (-0.003, 0.119) 0.056 (-0.014, 0.126) 0.050 (-0.021, 0.120) 0.056 (-0.001, 0.114)	Percentage reduction vs placebo (p value 129 ($p = 0.002$) 59 ($p = 0.665$) 83 ($p = 0.124$) 168 ($p = 0.064$) 121 ($p = 0.064$) 144 ($p = 0.116$) 84 ($p = 0.161$) 147 ($p = 0.055$) 188 ($p = 0.681$)
(b) Subgroups Age \leq 45 years Age \geq 45 years Disease duration \leq 15 years Disease duration \geq 15 years EDSS \leq 6.0 EDSS \geq 6.0 EDSS \geq 6.0 SDMT \geq 43 SDMT \leq 43 Non-active SPMS Active SPMS	Abso	lute change median Pla -0.0	e from I nMTR acebo 054 -0.038 -0.039 58 -0.038	-0.009	to M24 in nimod 0.032 0.010 0.017 0.018	n/n (siponimod/ placebo) 100/58 175/98 131/84 144/72 133/78 142/78 111/74 159/82 129/71 146/85	Between-treatment difference (95% Cl) 0.174 (0.071, 0.277) 0.010 (-0.036, 0.056) 0.045 (-0.013, 0.103) 0.064 (-0.004, 0.131) 0.058 (-0.003, 0.119) 0.056 (-0.014, 0.126) 0.050 (-0.021, 0.120) 0.056 (-0.001, 0.114) 0.015 (-0.058, 0.088) 0.084 (0.031, 0.136)	Percentage reduction vs placebo (p value 129 ($p = 0.002$) 59 ($p = 0.665$) 83 ($p = 0.124$) 168 ($p = 0.064$) 121 ($p = 0.064$) 144 ($p = 0.116$) 84 ($p = 0.161$) 147 ($p = 0.055$) 188 ($p = 0.681$) 112 ($p = 0.002$)
(b) Subgroups Age \leq 45 years Age \geq 45 years Disease duration \leq 15 years Disease duration \geq 15 years EDSS \leq 6.0 EDSS \geq 6.0 SDMT \geq 4.3 SDMT \leq 4.3 Non-active SPMS Active SPMS Without superimposed relats	Abso -0.134	lute change median Pte -0.0 -0.0 -0.0	¢ from l nMTR acebo 054 -0.038 -0.038 -0.038	-0.009	to M24 in nimod 0.035 0.010 0.017 0.018 0.007 0.009	n/n (siponimod/ placebo) 100/58 175/98 131/84 144/72 133/78 142/78 142/78 111/74 159/82 129/71 146/85 163/81	Between-treatment difference (95% Cl) 0.174 (0.071, 0.277) 0.010 (-0.036, 0.056) 0.045 (-0.013, 0.103) 0.064 (-0.004, 0.131) 0.058 (-0.003, 0.119) 0.056 (-0.014, 0.126) 0.050 (-0.021, 0.120) 0.056 (-0.001, 0.114) 0.015 (-0.058, 0.088) 0.084 (0.031, 0.136) 0.033 (-0.031, 0.096)	Percentage reduction vs placebo (p value 129 ($p = 0.002$) 59 ($p = 0.665$) 83 ($p = 0.124$) 168 ($p = 0.064$) 121 ($p = 0.064$) 144 ($p = 0.116$) 84 ($p = 0.161$) 147 ($p = 0.055$) 188 ($p = 0.681$) 112 ($p = 0.002$) 165 ($p = 0.306$)
(b) Subgroups Age \leq 45 years Age $>$ 45 years Disease duration \leq 15 years Disease duration $>$ 15 years EDSS $<$ 6.0 EDSS \geq 6.0 SDMT $>$ 43 SDMT \leq 43 Non-active SPMS Active SPMS Without superimposed relapses	Abso -0.134	lute change median Pte -0.0	¢ from l nMTR acebo 054 -0.038 -0.038 -0.039 58 -0.038	-0.009	to M24 in nimod 0.035 0.010 0.017 0.018 0.007 0.009 0.013	n/n (siponimod/ placebo) 100/58 175/98 131/84 144/72 133/78 142/78 142/78 111/74 159/82 129/71 146/85 163/81 112/75	Between-treatment difference (95% Cl) 0.174 (0.071, 0.277) 0.010 (-0.036, 0.056) 0.045 (-0.013, 0.103) 0.064 (-0.004, 0.131) 0.056 (-0.014, 0.126) 0.050 (-0.021, 0.120) 0.056 (-0.001, 0.114) 0.015 (-0.058, 0.088) 0.084 (0.031, 0.136) 0.033 (-0.031, 0.096) 0.071 (0.010, 0.131)	Percentage reduction vs placebo (p value 129 ($p = 0.002$) 59 ($p = 0.665$) 83 ($p = 0.124$) 168 ($p = 0.064$) 121 ($p = 0.064$) 144 ($p = 0.116$) 84 ($p = 0.161$) 147 ($p = 0.055$) 188 ($p = 0.681$) 112 ($p = 0.002$) 165 ($p = 0.306$) 97 ($p = 0.024$)
(b) Subgroups Age \leq 45 years Age \geq 45 years Disease duration \leq 15 years Disease duration \geq 15 years EDSS \leq 6.0 EDSS \geq 6.0 SDMT \geq 4.3 SDMT \leq 4.3 Non-active SPMS Active SPMS Without superimposed relapses Without G4+ lesions	Abso -0.134	lute change median Pte -0.0 -0.	¢ from h nMTF acebo 054 -0.038 0.048 -0.039 58 -0.039 -0.038	-0.009 -0.009 -0.009 -0.009 -0.009	to M24 in nimod 0.035	n/n (siponimod/ placebo) 100/58 175/98 131/84 144/72 133/78 142/78 142/78 111/74 159/82 129/71 146/85 163/81 112/75 218/126	Between-treatment difference (95% Cl) 0.174 (0.071, 0.277) 0.010 (-0.036, 0.056) 0.045 (-0.013, 0.103) 0.064 (-0.004, 0.131) 0.056 (-0.014, 0.126) 0.050 (-0.021, 0.120) 0.056 (-0.001, 0.114) 0.015 (-0.058, 0.088) 0.084 (0.031, 0.136) 0.033 (-0.031, 0.096) 0.071 (0.010, 0.131) 0.037 (-0.016, 0.089)	Percentage reduction vs placebo (p value 129 ($p = 0.002$) 59 ($p = 0.665$) 83 ($p = 0.124$) 168 ($p = 0.064$) 121 ($p = 0.064$) 144 ($p = 0.116$) 84 ($p = 0.161$) 147 ($p = 0.055$) 188 ($p = 0.681$) 112 ($p = 0.002$) 165 ($p = 0.306$) 97 ($p = 0.024$) 116 ($p = 0.168$)
(b) Subgroups Age \leq 45 years Age $>$ 45 years Disease duration \leq 15 years Disease duration $>$ 15 years EDSS $<$ 6.0 EDSS \geq 6.0 SDMT $>$ 43 SDMT \leq 43 Non-active SPMS Active SPMS Without superimposed relapses With superimposed relapses Without Gd+ lesions With Gd+ lesions	Abso	lute change median Pla -0.1 -0.075 -0.075 -0.072	2 from h nMTR acebo 	-0.009	to M24 in nimod 0.036 0.010 0.017 0.007 0.009 0.013 0.005 0.014	n/n (siponimod/ placebo) 100/58 175/98 131/84 144/72 133/78 142/78 142/78 111/74 159/82 129/71 146/85 163/81 112/75 218/126 57/30	Between-treatment difference (95% Cl) 0.174 (0.071, 0.277) 0.010 (-0.036, 0.056) 0.045 (-0.013, 0.103) 0.064 (-0.004, 0.131) 0.056 (-0.014, 0.126) 0.050 (-0.021, 0.120) 0.056 (-0.001, 0.114) 0.015 (-0.058, 0.088) 0.084 (0.031, 0.136) 0.033 (-0.031, 0.096) 0.071 (0.010, 0.131) 0.037 (-0.016, 0.089) 0.114 (0.038, 0.190)	Percentage reduction vs placebo (p value 129 ($p = 0.002$) 59 ($p = 0.665$) 83 ($p = 0.124$) 168 ($p = 0.064$) 121 ($p = 0.064$) 144 ($p = 0.161$) 147 ($p = 0.055$) 188 ($p = 0.681$) 112 ($p = 0.002$) 165 ($p = 0.306$) 97 ($p = 0.024$) 116 ($p = 0.168$) 114 ($p = 0.055$)

Figure 5, (Continued)

(C) Subaroups		Placeho	Sinor	aimod	n/n (siponimod/ placebo)	Between-treatment difference (95% CI)	Percentage reduction vs placebo (p value)
Age ≤ 45 years	-0.122	100000			100/58	0.138 (0.047, 0.228)	112 (p = 0.004)
Age > 45 years		-0.03	6	0.008	175/98	0.044 (0.005, 0.082)	122 (p = 0.027)
Disease duration ≤ 15 years	-0.	064	-0.007		131/84	0.057 (0.007, 0.107)	89 (p = 0.026)
Disease duration > 15 years		-0.048	-0.001	0.026	144/72	0.075 (0.020, 0.129)	154 (p = 0.008)
EDSS < 6.0	-0	.061		0.009	133/78	0.070 (0.018, 0.122)	115 (<i>p</i> = 0.009)
EDSS ≥ 6.0		-0.041		0.013	142/78	0.054 (0.000, 0.108)	132 (p = 0.049)
SDMT > 43	-	0.055		0.000	111/74	0.055 (0.007, 0.103)	100 (p = 0.026)
SDMT ≤ 43		-0.049		0.018	159/82	0.066 (0.013, 0.119)	137 (p = 0.014)
Non-active SPMS		-0.042		0.04	_{.0} 129/71	0.083 (0.017, 0.149)	195 (<i>p</i> = 0.015)
Active SPMS	-0.07	70	-0.002		146/85	0.067 (0.027, 0.107)	97 (<i>p</i> = 0.001)
Without superimposed relapse	es	-0.041		0.027	163/81	0.068 (0.014, 0.122)	166 (<i>p</i> = 0.014)
With superimposed relapses	-0.074		-0.014		112/75	0.060 (0.013, 0.107)	81 (<i>p</i> = 0.013)
Without Gd+ lesions		-0.047		0.014	218/126	0.062 (0.018, 0.105)	130 (<i>p</i> = 0.006)
With Gd+ lesions	-0.081	-	_	0.014	57/30	0.095 (0.034, 0.156)	117 (<i>p</i> = 0.003)
	–0.150 –0.100 Absolute chang media	–0.05 ge from I n nMTR	50 (baseline f in NAWN	0 0.05 to M24 in /	0	Subgroups by disease Subgroups by inflamma	history and severity atory disease activit

Figure 5. Change in median nMTR from baseline to 24 months in (a) NABT, (b) cGM, and (c) NAWM by subgroups according to baseline age, disease duration, severity, or activity^a (PPS^b).

cGM: cortical gray matter; CI: confidence interval; EDSS: Expanded Disability Status Scale; FAS: full analysis set; Gd+: gadoliniumenhancing; M: month; NABT: normal-appearing brain tissue; NAWM: normal-appearing white matter; nMTR: normalized magnetization transfer ratio; PPS: per-protocol set; SDMT: Symbol Digit Modalities Test; SPMS: secondary progressive multiple sclerosis. ^aPatients were considered to have active SPMS if they had \geq 1 relapse in the 2 years before the study and/or had \geq 1 Gd+ lesion at baseline; superimposed relapses and Gd+ lesions subgroups are based on events 2 years before or at baseline, respectively. ^bPPS included all patients from the FAS who did not have any major protocol deviations that could confound interpretation.

Nevertheless, the effect of siponimod was consistent in patients with or without inflammatory disease activity (i.e. gadolinium-enhancing lesions). Thus, these findings all together suggest that the action of siponimod is being mediated (at least in part) independently of effects on acute inflammation. Reductions in GM atrophy have been associated with positive effects on long-term clinical outcomes, including disability progression and cognitive decline.^{8–10} The reduced GM atrophy observed here contributes to the previous reported delays in progression of physical disability and cognitive impairment observed with siponimod versus placebo in EXPAND.^{24,25} Interestingly, other potent antiinflammatory DMTs such as natalizumab did not show conclusive effects on these measures in patients with SPMS.31 Ocrelizumab reported significant effects on thalamic atrophy but no significant effects in reducing cGM atrophy in patients with progressive MS.32

Siponimod positively affected brain tissue integrity/ myelination (assessed by nMTR), consistently slowing nMTR decrease over 24 months in NABT (by 70%-170%), cGM (by 59%-188%), and NAWM (by 81%-195%). This effect was most pronounced in NAWM, in which a significant increase in nMTR relative to placebo was observed in most subgroups. Importantly, diffuse injury in NAWM is closely associated with cortical lesion volume.3 Effects on nMTR became more pronounced over time, with nMTR returning to or surpassing baseline in patients treated with siponimod. Although MTR increases may be associated with resolution of edema, the changes reported here were made in normal-appearing tissues, which are not subject to large changes in water content, and in acute lesions with reference to stable pre-lesion and post-lesion levels. Under these circumstances, the recovery of inflammatory edema associated with acute lesions is not relevant, and these changes could be interpreted as reflecting improvements in myelin density and tissue integrity. This is supported by the fact that nMTR recovered to a greater extent with siponimod than with placebo even in patients without inflammatory disease activity. The fact that the treatment effect on nMTR only became apparent during the second year of treatment suggests that measures of neurodegeneration and

Table 2. nMTR recovery in nMTR lesions (FASa).

	Siponimod (<i>N</i> =413, <i>N</i> '=72)	Placebo (<i>N</i> =226, <i>N</i> '=80)	Treatment difference (siponimod vs placebo)	<i>p</i> -value
nMTR drop (accounting for lesion volume)	-1.35	-1.71	0.36	< 0.0001

FAS: full analysis set; MTR: magnetization transfer ratio; N: number of patients in MTR subset; N': number of patients with at least one MTR lesion; nMTR: normalized magnetization transfer ratio.

nMTR drop (i.e. nMTR recovery metrics) describes the total decrease in nMTR from pre- to post-nMTR lesion time points. At least three MTR scans were needed: (1) to obtain a stable pre-lesion nMTR value; (2) to detect an acute drop in nMTR indicative of a newly forming lesion; and (3) to obtain a stable post-lesion nMTR value. In this analysis, the latest available measurement before the formation of a new lesion was taken as pre-lesion time point, and the latest available measurement after the formation of a new lesion was taken as the post-lesion time point. Peri-lesion time points were not included.

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





FAS: full analysis set; GM: gray matter; MTR: magnetization transfer ratio; nMTR: normalized magnetization transfer ratio; WM: white matter.

nMTR drop (i.e. nMTR recovery metrics) describes the total decrease in nMTR from pre- to post-nMTR lesion time points. ^aFAS included all randomized patients with assigned treatments who took at least one dose of study medication.

neuroprotective mechanisms may need to be monitored over a relatively long time before becoming detectable. The fact that siponimod improved nMTR recovery in newly formed nMTR lesions is consistent with observations from preclinical studies showing that siponimod promotes remyelination.^{22,33}

There is little precedence in the clinical trial literature of currently approved DMTs for the observations reported here with siponimod in patients with SPMS. Other DMTs have been reported to slow cortical and thalamic GM atrophy mainly in relapsing MS.^{32,34} Reports of increased MTR levels have been made in relapsing MS, where dimethyl fumarate has been shown to increase MTR in normal-appearing tissues²⁷

but not in newly formed lesions, and not in SPMS. Observations from preclinical models support a promyelinating effect of siponimod.^{22,33} Taken together with the findings from this study, siponimod may have an impact on the neurodegenerative component of SPMS (in addition to anti-inflammatory effects) that may have contributed to the reduced risk of disability progression and of cognitive worsening observed with siponimod versus placebo in EXPAND. Most DMTs approved for relapsing MS, including highly effective anti-inflammatory drugs such as natalizumab,³¹ failed to slow disability progression when studied in SPMS or primary progressive multiple sclerosis (PPMS). Conversely, ibudilast, a DMT in development, was associated with benefits on markers of neurodegeneration but not on markers of acute inflammation in a phase 2 trial in patients with progressive MS.³⁵ Thus, therapeutic action on inflammation and neurodegeneration is de-coupled in other DMTs. As shown in clinical and preclinical studies, siponimod appears to affect both neurodegeneration/ demyelination and inflammation, consistent with a dual mode of action.

A few limitations to this study are important to appreciate. Brain volume changes on the order of a fraction of a percent can result from causes other than irreversible neurodegeneration, and the subtle increases in brain volume observed here could reflect increases in the volume of glial cells, and not necessarily neuronal cells (although this may still be an important neuroprotective effect). Similarly, the changes in MTR, although relatively specific for myelin, are associated with changes in other tissue components, which tend to change in a correlated fashion. Changes in tissue water can be associated with small changes in brain volume or MTR simply because of dilution or concentration. However, for this effect to be responsible for the observations reported here, increases in MTR would have to have been associated with increased atrophy, which was not the case. Considering that MRI scans in this study were scheduled annually, it was not possible to determine the exact time of onset of lesion formation for all MTR lesions. This analysis also relied on the assumption that MTR values were stable outside the period of acute lesion formation and recovery.

In summary, these beneficial effects of siponimod on regional brain atrophy and tissue integrity/myelination are consistent with previous preclinical findings and highlight possible direct CNS effects of siponimod, which may be relevant to its effects on disability progression and cognitive processing speed in patients with SPMS.

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Supplemental material

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