

Long-term Effect of Siponimod on MRI Outcomes in SPMS: Analyses from the EXPAND Study up to 5 Years



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Introduction

- Siponimod selectively modulates S1P (1,5) receptors^{1,2} which are expressed on peripheral lymphocytes and within the central nervous system on the neurons and glial cells³
- Several preclinical studies have demonstrated that siponimod has direct effects in the CNS, eliciting beneficial effects on inflammation, neurodegeneration and remyelination⁴⁻⁹
- In the Phase 3 EXPAND core study, siponimod compared with placebo significantly reduced the risk of disability progression, showed benefits in cognitive processing speed, and MRI measures of focal inflammation and neurodegeneration (GM atrophy and MTR) in a broad population of patients with SPMS^{10,11}

Objective

- Here, we use data from the core part+extension part of the EXPAND study to investigate the long-term effect of siponimod on MRI measures of inflammation and neurodegeneration including:
 - Lesion-based MRI parameters: change in T2LV and cumulative new/enlarging T2 lesions
 - Brain volume loss: total brain and grey matter (cGM and thalamic atrophy as measures of neurodegeneration)

Methods

- The core part was a variable treatment duration and event-driven study and of 1651 patients randomized in the core part (aged 18 to 60 years), 1224 entered the extension part
 - Patients receiving siponimod 2 mg/day continued to receive siponimod (continuous siponimod group)
 - Patients receiving placebo in core part were switched to receive siponimod 2 mg/day in the extension part (placebo-siponimod switch group).
- Given the event-driven design, time in the core part varied from 12 and up to 37 months for individual patients (median duration 21 months) before transitioning to the extension part (transition period between M12 and M36)
- **Between-group comparisons:** changes in MRI from core part baseline (M0) through M60 (core+extension parts) were compared between the continuous siponimod group and the placebo-siponimod switch group
- **Within-group comparisons:*** changes in MRI outcomes within each treatment group during the core part and during the extension part
 - To account for the variable exposure time, annualized measures of the MRI parameters were assessed for the first 12 months of core part and the first 12 months of extension part, as well as for the total duration of extension part (median 36 months) and total duration of core part (median 21 months):
 - Yearly average for T2LV change and new/enlarging T2 counts
 - Annualized rate of brain atrophy (ARBA) for rate of brain volume loss
- Treatment effects were determined using MMRM or Wilcoxon signed-rank test

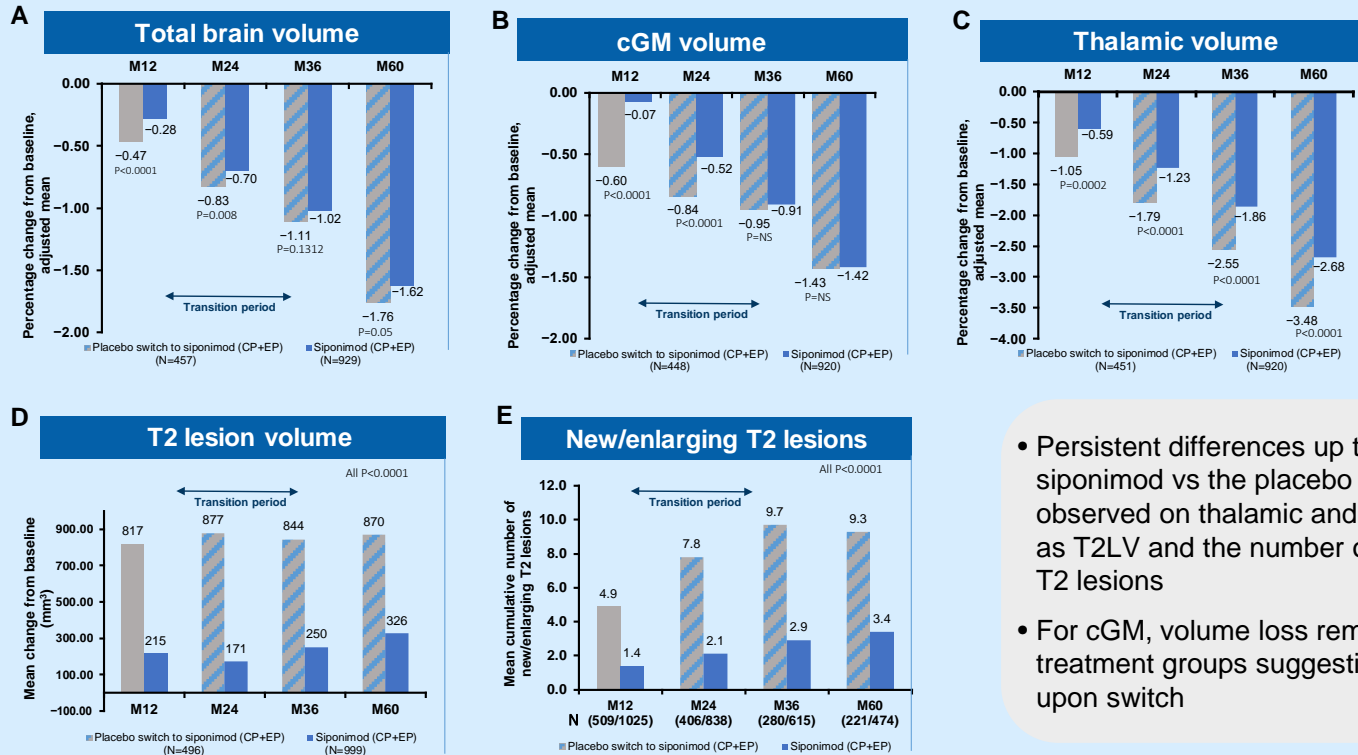
*The percent change relative to start of EP was derived accounting for the change during the CP

cGM, cortical gray matter; CP, core part; CNS, central nervous system; EP, extension part; GM, gray matter; M, months; MMRM, mixed model of repeated measures; MRI, magnetic resonance imaging; MTR, magnetization transfer ratio; SPMS, secondary progressive multiple sclerosis; S1P, sphingosine 1-phosphate; T2LV, T2 lesion volume

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Results

Between-group comparison: Placebo-siponimod vs continuous siponimod from CP baseline by timepoint



■ Placebo before switch to siponimod (M12)

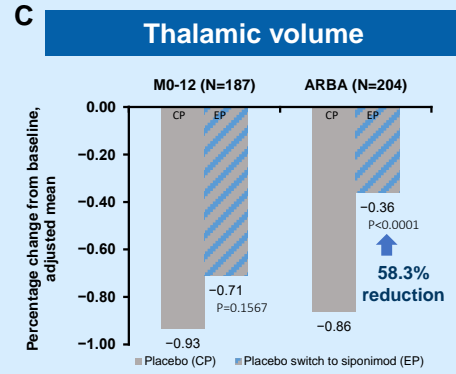
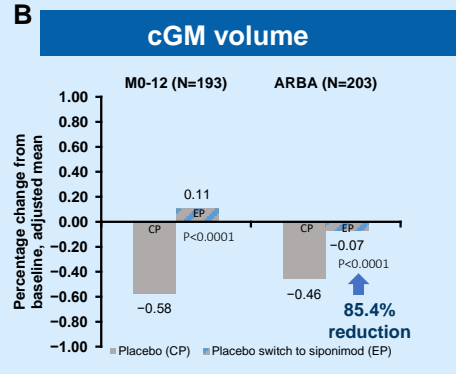
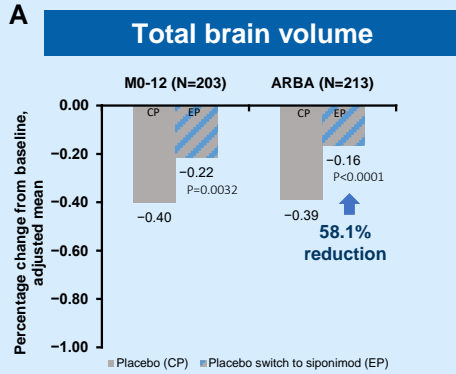
- Persistent differences up to M60 favoring continuous siponimod vs the placebo switch group were observed on thalamic and total brain volume as well as T2LV and the number of new/enlarging T2 lesions
- For cGM, volume loss remained low in both treatment groups suggesting an immediate benefit upon switch

A-D: MMRM model — percent change from baseline adjusted for visit, treatment, age, number of Gd+ T1 lesions at baseline, T2 lesion volume (cm³) at baseline, superimposed relapses at baseline, visit*treatment interaction (and baseline normalized brain tissue volume, where applicable); E: p-values from Wilcoxon rank sum test for differences between treatment groups

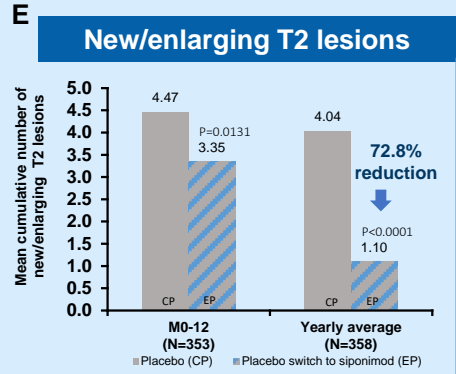
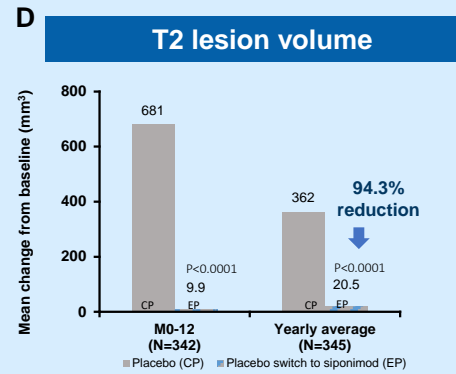
cGM, cortical gray matter; CP, core part; EP, extension part; Gd, Gadolinium; M, months; MMRM, mixed model for repeated measures; MRI, magnetic resonance imaging; N, number of patients; NS, not significant; T2LV, T2 lesion volume

Results

Within-group comparison: Placebo-siponimod switch group



ARBA is derived from percent change to last visit during CP (median 21 months) and during EP (median 36 months)



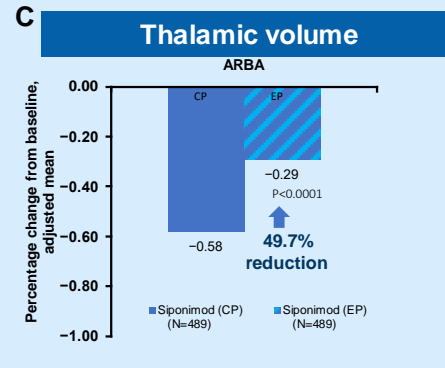
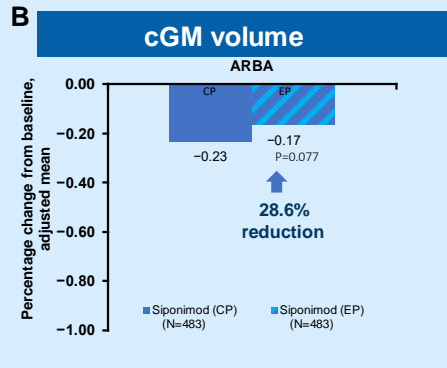
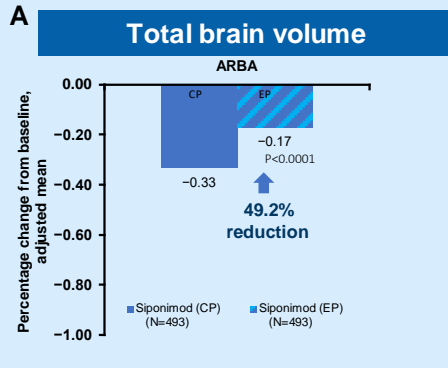
- A significant improvement was observed on all MRI measures upon switching from placebo in the core part to siponimod in the extension part
- There was a complete suppression of cGM atrophy and no increase in T2 lesion volume within the first 12 months upon switch from placebo to siponimod (M0–12 of the extension part)

At each time point, only patients with a value both at the CP visit and the corresponding EP visit are included; the yearly average is derived by standardizing the change to the last visit to 360 days p-values from Wilcoxon signed-rank test comparing percent changes between CP and EP within each group

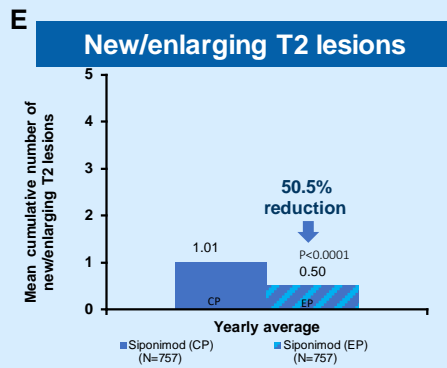
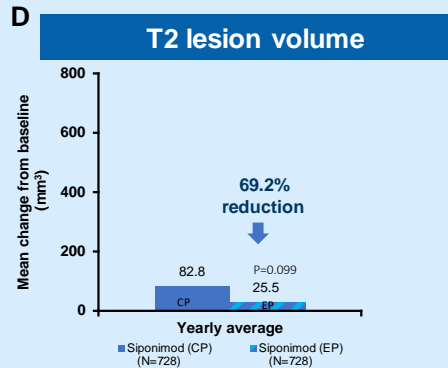
ARBA, annualized rate of brain atrophy; cGM, cortical grey matter; CP, core part; EP, extension part; M, months; MRI, magnetic resonance imaging; N, number of patients; T2LV, T2 lesion volume

Results

Within-group comparison: Continuous siponimod group



ARBA is derived from percent change to last visit during CP (median 21 months) and during EP (median 36 months)



- In the continuous siponimod group, benefit on all MRI measures was maintained during the extension part
- The low levels of BV loss, thalamic volume loss and T2 lesion activity observed in the core part were significantly lowered further in the extension part

At each time point, only patients with a value both at the CP visit and the corresponding EP visit are included; the yearly average is derived by standardizing the change to the last visit to 360 days p-values from Wilcoxon signed-rank test comparing percent changes between CP and EP within each group

ARBA, annualized rate of brain atrophy; BV, brain volume; cGM, cortical gray matter; CP, core part; EP, extension part; MRI, magnetic resonance imaging; N, number of patients

Conclusions

- Siponimod treatment showed sustained efficacy on MRI parameters of inflammation and neurodegeneration (brain tissue atrophy including GM) over the long term in the EXPAND SPMS population
- In the continuous siponimod group, the low rate of brain tissue atrophy and lesion activity were maintained, and some parameters were significantly reduced further during the extension part, suggesting continued efficacy on those MRI outcomes over the long term
- Patients switching from placebo to siponimod in the extension part recapitulated pronounced reductions in the rate of brain atrophy and lesion activity with a complete suppression of cGM atrophy and no increase in T2 lesion volume within 12 months of starting siponimod
- Persistent differences between continuous and switch groups in measures of brain tissue integrity highlight the importance of early treatment initiation

Disclosures

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