

Effect of siponimod on cognitive processing speed in SPMS patients with active and non-active disease

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Disclosures

Iris-Katharina Penner has received honoraria for speaking at scientific meetings, serving at scientific advisory boards and consulting activities from Adamas Pharma, Almirall, Bayer Pharma, Biogen, Celgene, Desitin, Sanofi-Genzyme, Janssen, Merck Serono GmbH, an affiliate of Merck KGaA, Novartis, Roche, and Teva. She has received research support from the German MS Society, Celgene, Roche, Teva, and Novartis.

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, 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).

Bruce A.C. Cree has received personal compensation for consulting from AbbVie, Akili, Alexion, Biogen, EMD Serono, Novartis, Sanofi Genzyme and TG Therapeutics.

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Amit Bar-Or has participated as a speaker in meetings sponsored by and received consulting fees and/or grant support from: Janssen/Actelion, Atara Biotherapeutics, Biogen Idec, Celgene/Receptos, Roche/Genentech, MedImmune, Merck/EMD Serono, Novartis, Sanofi-Genzyme.

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Thomas Hach, Göril Karlsson, Shannon Ritter, Nicolas Rouyrre and Daniela Piani Meier are employees of Novartis.

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Background and objective

- Cognitive impairment is present in all MS subtypes from clinical onset, but is more common among patients with SPMS than patients with RRMS, affecting up to 80% of patients with SPMS¹⁻³
- Symbol Digit Modalities Test is considered the most reliable and sensitive measure for assessing cognitive processing speed and is the preferred metric in MS trials^{4,5}
- In the EXPAND Phase III study in SPMS patients, siponimod significantly reduced 3mCDP by 21% and 6mCDP by 26% versus placebo and showed significant and clinically meaningful^a benefits on cognitive processing speed as measured by the SDMT^{6,7}

Objective

The effect of siponimod on cognitive processing speed in subgroups of patients with active^b and non-active^c disease from the EXPAND Core study was evaluated by:

Endpoints

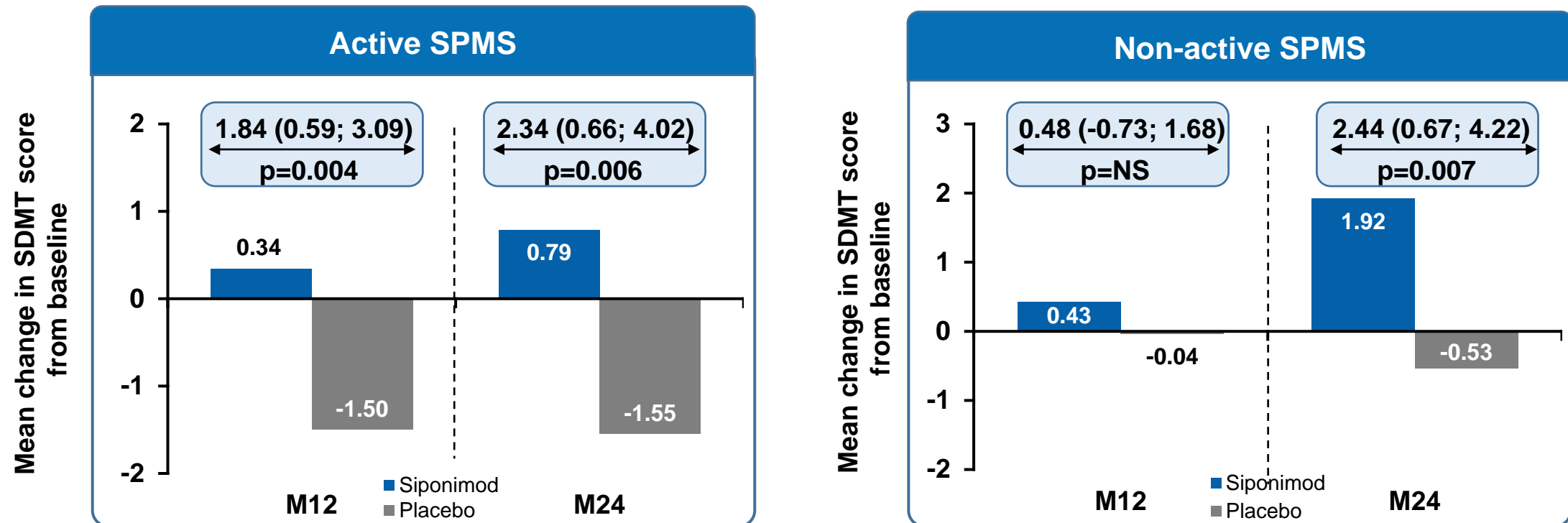
1. Change in SDMT scores from baseline
2. Time to 6-month confirmed clinically meaningful worsening or improvement (≥ 4 points)
3. Proportion of patients with worsened and improved SDMT scores (≥ 4 points)

^aa change in raw SDMT score by ≥ 4 points or 10% is clinically meaningful; ^bpatients with presence of relapses in the 2 years before screening and/or ≥ 1 T1 gadolinium-enhancing lesions at baseline (placebo [n=263], siponimod [n=516]); ^cpatients with no relapse in prior 2 years and no gadolinium-enhancing lesions at baseline (counterpart of active patients; placebo [n=270], siponimod [n=557])
3mCDP, 3-month confirmed disability progression; 6mCDP, 6-month confirmed disability progression; CPS, cognitive processing speed; m, month; MS, multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis; SDMT, Symbol Digit Modalities Test; SPMS, secondary progressive multiple sclerosis

1. Ruano L, et al. *Mult Scler.* 2017;23:1258-67; 2. Matias-Guiu JA, et al. *Front. Neurol.* 2017;8:643; 3. Chiaravalloti ND and DeLuca J. *Lancet Neurol.* 2008;7:1139-1151; 4. Strober L, et al. *Mult Scler.* 2019;25:1781-1790; 5. Benedict, et al. *Mult Scler* 2017;23:721-733. 6. Kappos L, et al. *Lancet.* 2018;391:1263–1273; 7. Benedict RHB, et al. Presented at AAN 2018. S44.004.



Effect of siponimod on change in SDMT from baseline to Month 12 and Month 24

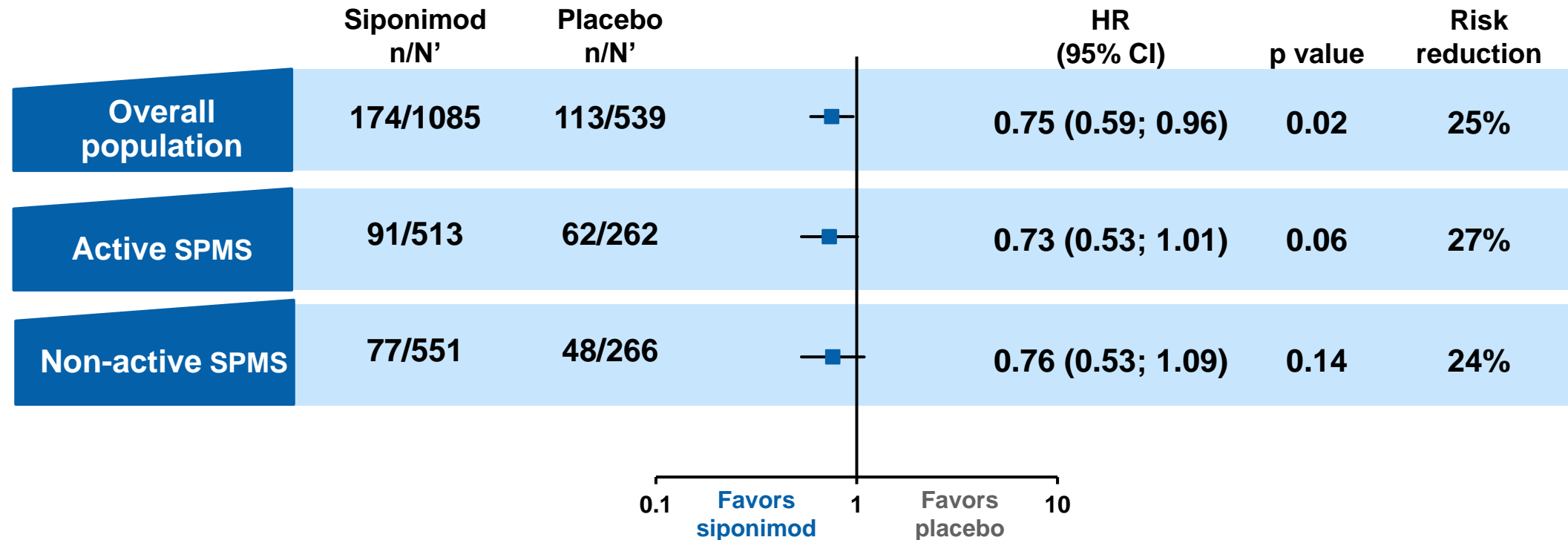


Overall population (between group difference), M12: 1.05 (0.20; 1.91, p=0.016); M24: 2.28 (1.09; 3.48), p<0.001

Siponimod was associated with significantly improved mean changes from baseline to M24 in SDMT scores versus placebo in patients with active and non-active disease, consistent with the overall population



Effect of siponimod on 6m-confirmed clinically meaningful^a worsening in cognitive processing speed

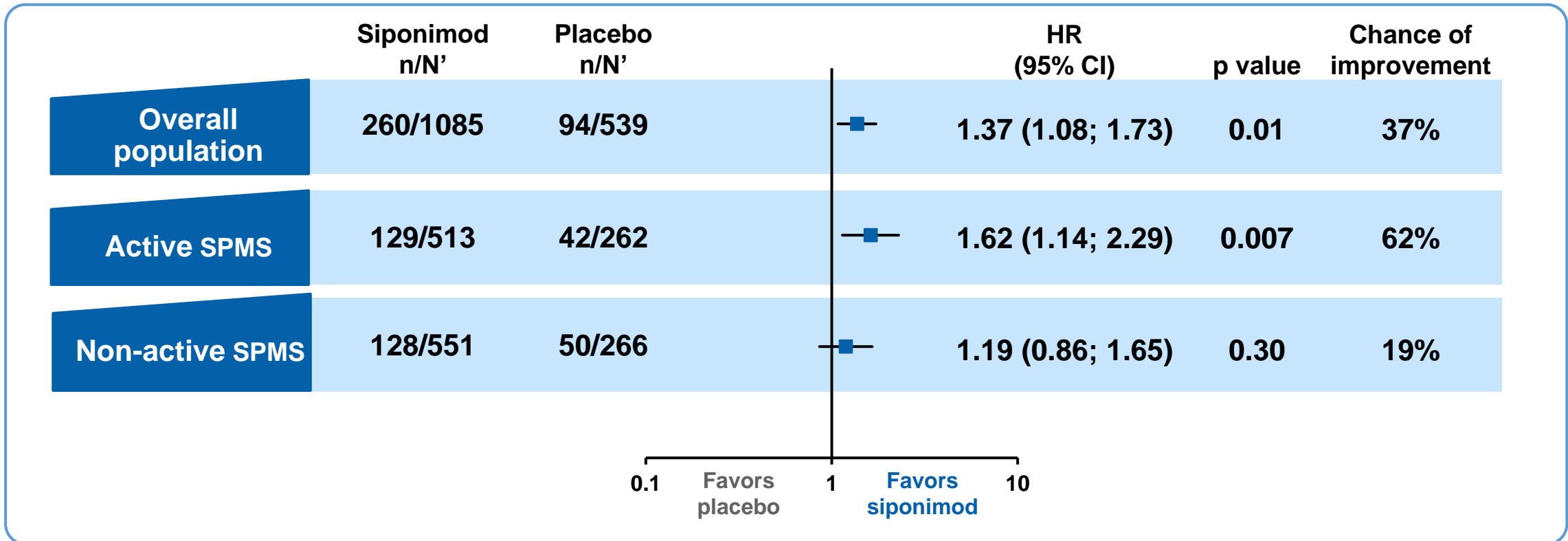


Siponimod reduced the risk of 6-month confirmed clinically meaningful worsening by 24% to 27% versus placebo across all groups studied

^a>4 points change in SDMT score; data were analyzed by Cox regression model adjusted for predictors treatment and baseline SDMT and baseline MSSS
n, number of patients with event; N', number of patients included in the analysis; HR, hazard ratio; SDMT, Symbol Digit Modalities Test; SPMS, secondary progressive multiple sclerosis



Effect of siponimod on 6m-confirmed clinically meaningful^a improvement in cognitive processing speed

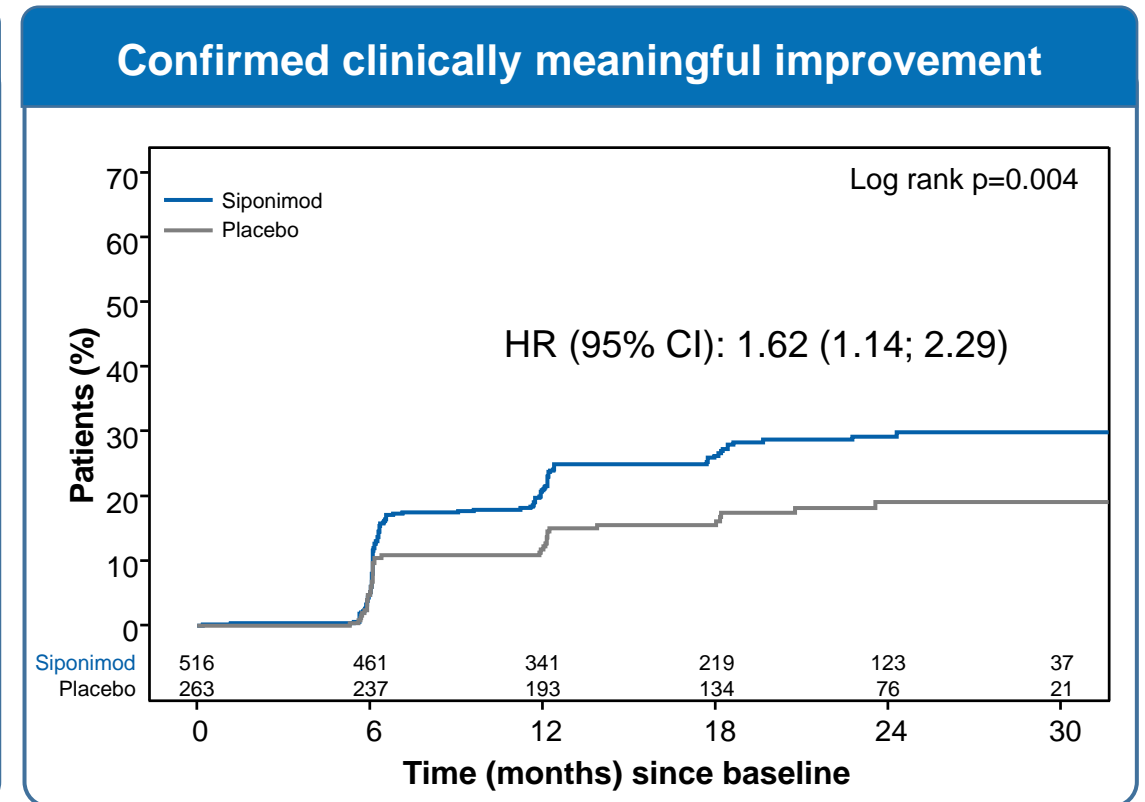
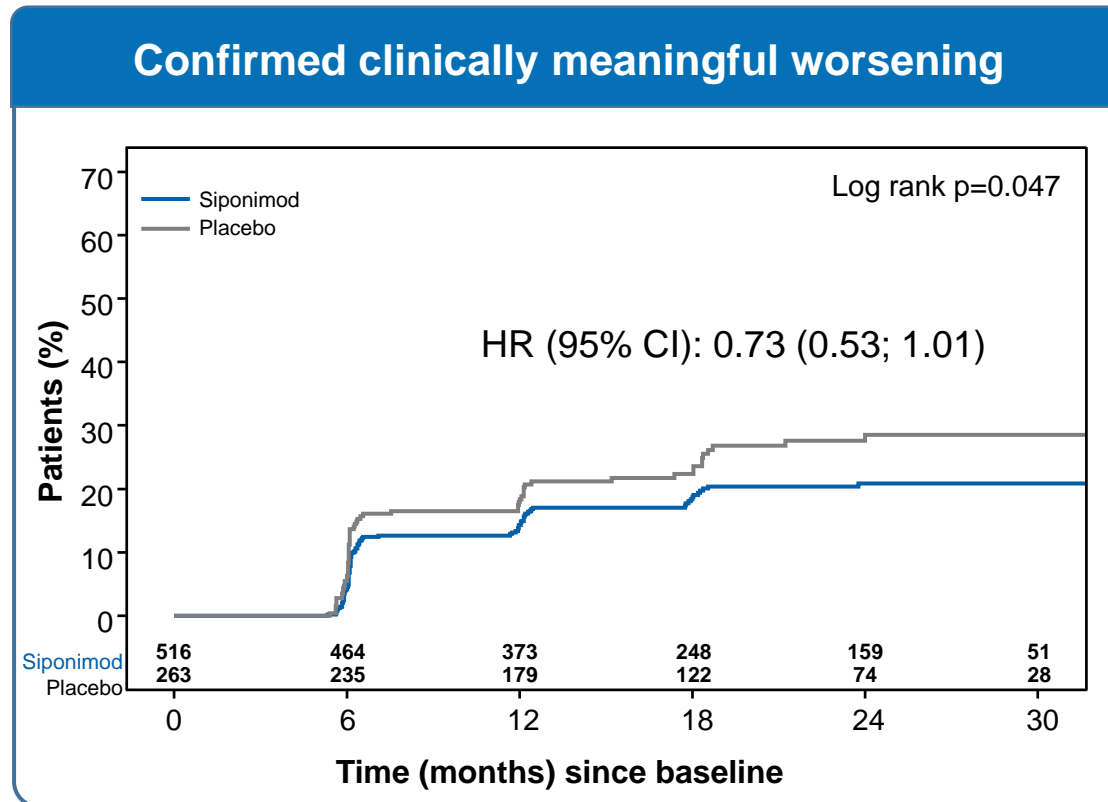


Siponimod significantly increased the chance of 6-month confirmed clinically meaningful improvement versus placebo in the active group, consistent with the overall population with a non-significant trend in the non-active group

^a>4 points change in SDMT score; data were analyzed by Cox regression model adjusted for predictors treatment and baseline SDMT and baseline MSSS
n, number of patients with event; N', number of patients included in the analysis; HR, hazard ratio; SDMT, Symbol Digit Modalities Test; SPMS, secondary progressive multiple sclerosis



Time to 6-month confirmed clinically meaningful^a worsening and improvement in SPMS patients with active disease

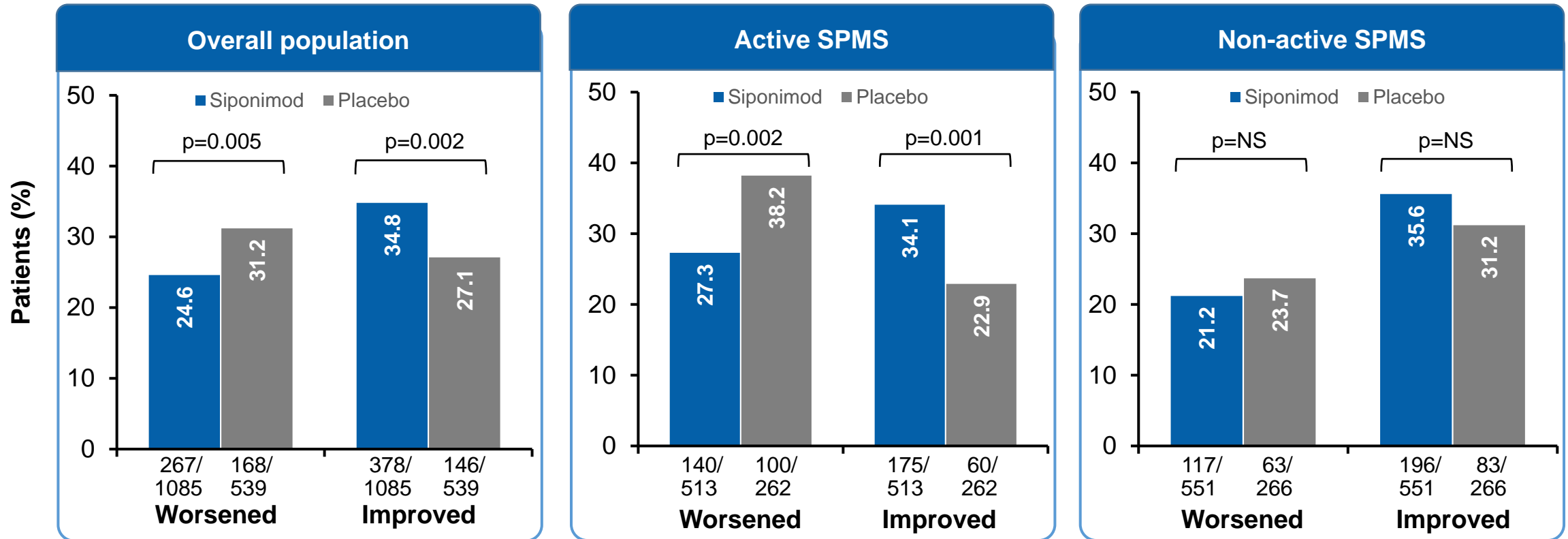


In SPMS patients with active disease, siponimod favorably impacted both time to 6-month confirmed clinically meaningful worsening and improvement

^a>4 points change in SDMT score; HR (95% CI) were calculated by Cox regression model adjusted for predictors treatment and baseline SDMT and baseline MSSS
 HR, hazard ratio; SPMS, secondary progressive multiple sclerosis



Proportion of patients with sustained^a clinically meaningful change in SDMT score during the EXPAND Core study^b

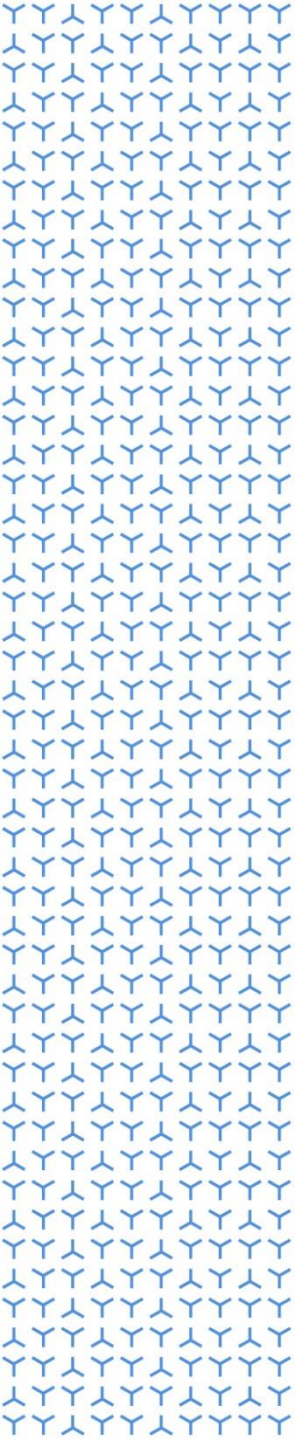


In the active SPMS group, a significantly lower proportion of patients worsened and significantly higher proportion of patients improved versus placebo. A similar but non-significant trend was observed in the non-active SPMS group

^a≥4-point change in the SDMT score from baseline that continued until the end of the follow-up in the Core part without ever returning to above or below this threshold; ^bmedian duration 21 months
Data were analyzed by Cox regression model adjusted for predictors treatment, country, baseline SDMT score, baseline MSSS and superimposed relapses at baseline; Comparison of categorical proportions was made using Chi square test; NS, not significant; SDMT, Symbol Digit Modalities Test; SPMS, secondary progressive multiple sclerosis

Conclusions

- **Over the 24 months of the EXPAND study, siponimod showed significant benefits in cognitive processing speed as measured by SDMT change from baseline in patients with both active and non-active SPMS**
- **The effects on clinically meaningful changes (≥ 4 points in the SDMT) were more pronounced in SPMS patients with active disease, where significantly fewer patients worsened and more patients improved with siponimod compared with the non-active group**
 - **A non-significant favorable trend was observed in the non-active group; longer observation may be necessary to detect meaningful changes (≥ 4 points) due to a slower progression rate in this group**



Thank you

