

# Effect of Siponimod on Disability Progression as Measured by the Ambulation Score, a Subscore of the Neurostatus-EDSS: Post hoc Analysis of the EXPAND Trial in SPMS

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## Disclosures

**Marcus D'Souza** received travel support from Bayer AG, Teva and Genzyme and research support from the University Hospital Basel • **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) • **Patrick Vermersch** received honoraria and consulting fees from Biogen, Sanofi-Genzyme, Novartis, Teva, Merck, Roche, Imcyse, AB Science and BMS-Celgene and research supports from Novartis, Sanofi-Genzyme and Roche • **Jeff Maca** is an employee of Novartis and may hold Novartis stocks • **Soudeh Ansari** is an employee of Novartis and may hold Novartis stocks • **Goeril Karlsson** is an employee of Novartis and may hold Novartis stocks • **Daniela Piani-Meier** is an employee of Novartis and may hold Novartis stocks • **Ludwig Kappos** has received the following exclusively for research support: Steering committee, advisory board, and consultancy fees (Actelion, Bayer HealthCare, Biogen, BMS, Genzyme, Janssen, Japan Tobacco, Merck, Novartis, Roche, Sanofi, Santhera, TG Therapeutics); Speaker fees (Bayer HealthCare, Biogen, Merck, Novartis, Roche, and Sanofi); Support of educational activities (Allergan, Bayer HealthCare, Biogen, CSL Behring, Desitin, Genzyme, Merck, Novartis, Roche, Pfizer, Sanofi, Shire, and Teva); License fees for Neurostatus products; And grants (Bayer HealthCare, Biogen, European Union, InnoSwiss, Merck, Novartis, Roche, Swiss MS Society, and Swiss National Research Foundation).

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- More than 50% of patients with RRMS transition to SPMS within 15–20 years, and disability continues to gradually worsen. Majority of currently available treatments did not consistently show efficacy in slowing disability progression independent of relapses
- Neurostatus-eEDSS is a standardized electronic neurological assessment to quantify disease related impairment and disability in patients with MS. It includes an automated real-time consistency-check and a digital expert-based review system. As part of Neurostatus.eEDSS the Ambulation Score (AS) provides a numerical score from 0 to 16, based on walking distance as assessed during the site visit and type of assistance required for walking<sup>1</sup>
- In the Phase 3 EXPAND study in patients with SPMS, siponimod significantly reduced the Neurostatus-EDSS-measured risk of 3/6-month confirmed disability progression versus placebo by 21%/26%, with more pronounced effects (31%/37%) in patients with active SPMS<sup>2</sup>

The image shows a screenshot of the Neurostatus-eEDSS assessment form. The form is divided into several sections: PERSONAL INFORMATION, NEUROSTATUS SCORING, CEREBELLAR FUNCTIONS, SENSORY EXAMINATION, BOWEL/BLADDER FUNCTIONS, CEREBRAL FUNCTIONS, MENTAL STATUS EXAMINATION, and AMBULATION. The AMBULATION section at the bottom includes fields for 'Distance reported by patient (in meters)', 'Assistance', 'Time reported by patient (in minutes)', 'Distance measured (in meters)', and 'AMBULATION SCORE'. A red arrow points from the 'AMBULATION' section of the Neurostatus-eEDSS form to the 'AMBULATION SCORE' section of the summary form.

## AMBULATION SCORE

- 0 Unrestricted
- 1 Fully ambulatory
- 2  $\geq 300$  meters, but  $< 500$  meters, without help or assistance (EDSS 4.5 or 5.0)
- 3  $\geq 200$  meters, but  $< 300$  meters, without help or assistance (EDSS 5.0)
- 4  $\geq 100$  meters, but  $< 200$  meters, without help or assistance (EDSS 5.5)
- 5 Walking range  $< 100$  meters without assistance (EDSS 6.0)
- 6 unilateral assistance,  $\geq 50$  meters (EDSS 6.0)
- 7 bilateral assistance,  $\geq 120$  meters (EDSS 6.0)
- 8 unilateral assistance,  $< 50$  meters (EDSS 6.5)
- 9 bilateral assistance,  $\geq 5$  meters, but  $< 120$  meters (EDSS 6.5)
- 10 Uses wheelchair without help; unable to walk 5 meters even with aid, essentially restricted to wheelchair; wheels self and transfers alone; up and about in wheelchair some 12 hours a day (EDSS 7.0)
- 11 Uses wheelchair with help; unable to take more than a few steps; restricted to wheelchair; may need some help in transferring and in wheeling self (EDSS 7.5)
- 12 essentially restricted to bed or chair or perambulated in wheelchair, but out of bed most of day; retains many self-care functions; generally has effective use of

<sup>1</sup>D'Souza M et al. Mult Scler. 2020 Jul;26(8):993-996

<sup>2</sup>Kappos L, et al., Lancet. 2018;391(10127):1263-1273;

## Objective

- To perform a post hoc analysis of the EXPAND trial data to assess the effect of siponimod on the AS of the Neurostatus-EDSS in patients with SPMS

## Methods

- EXPAND core part was a multi-center, randomized (2:1), double-blind, parallel-group, placebo-controlled, variable treatment duration, event-driven study in patients with SPMS<sup>1</sup> ([median (range) duration: 21 (0.2–37.0) months]):
  - The present analyses included all randomized subjects with assigned treatments who took at least one dose of study medication
  - The analyses comprised 1645 patients: 1099 in the siponimod group and 546 in the placebo group; active SPMS<sup>a</sup>/non-active SPMS<sup>b</sup> (Siponimod 516/557, placebo 267/270)
  - Median EDSS at baseline was 6.0
- The effect of siponimod on the EDSS and AS was evaluated by:
  - Difference in mean change in EDSS and AS from baseline was assessed using Jonckheere Terpstra test
  - Time-to-3 month and 6 month confirmed worsening on AS by  $\geq 1/\geq 2$ -points was assessed by Cox regression adjusted for treatment and baseline AS
  - Categorical changes: Mantel Haenszel chi-square test was used to assess the effect of treatment on proportion of patients with 6 month confirmed worsening or confirmed improvement by  $\geq 1$ -point during the core study

<sup>a</sup>presence of relapses in the 2 years prior to screening and/or  $\geq 1$  T1 gadolinium-enhancing lesion at baseline

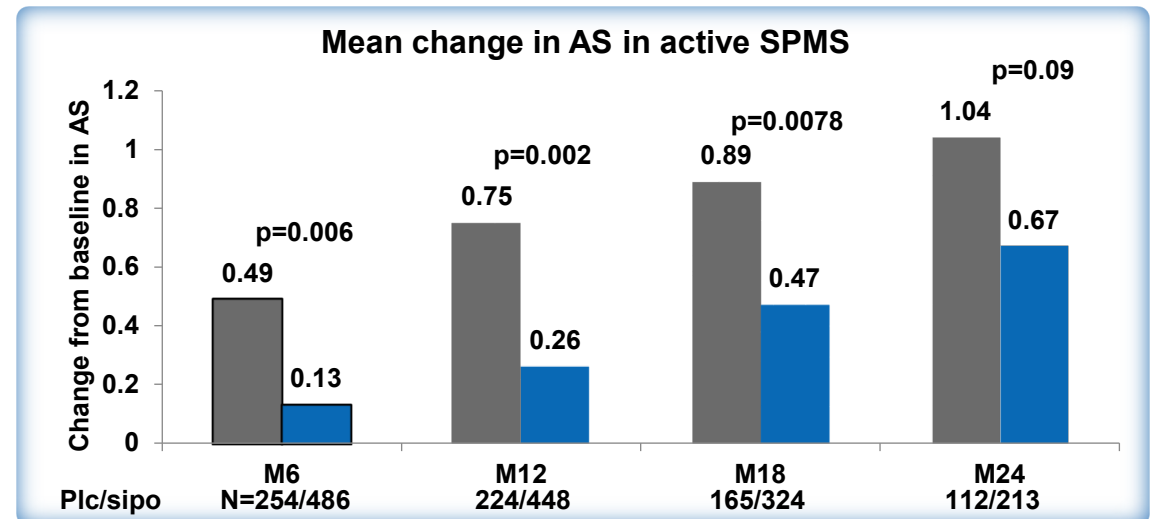
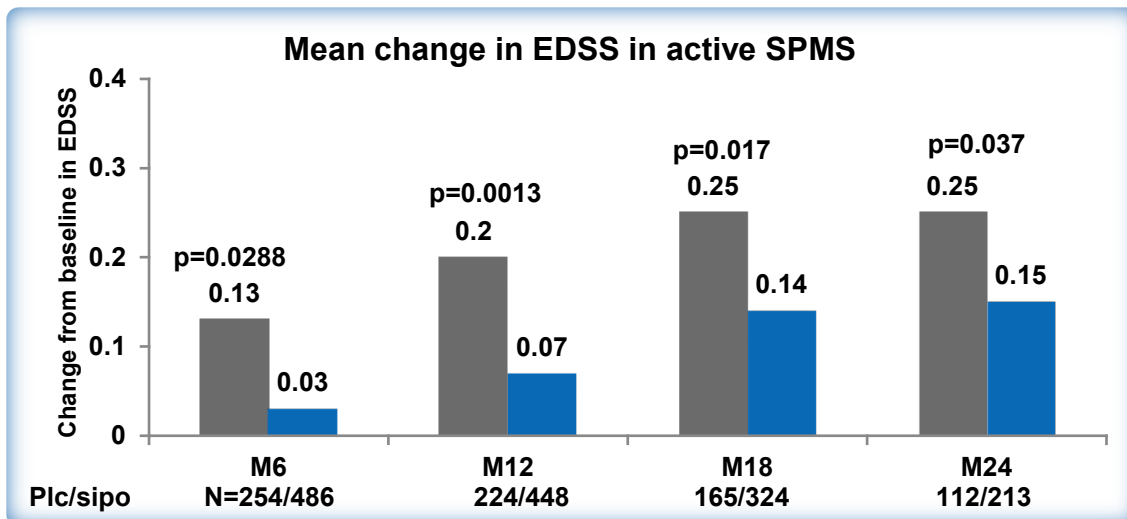
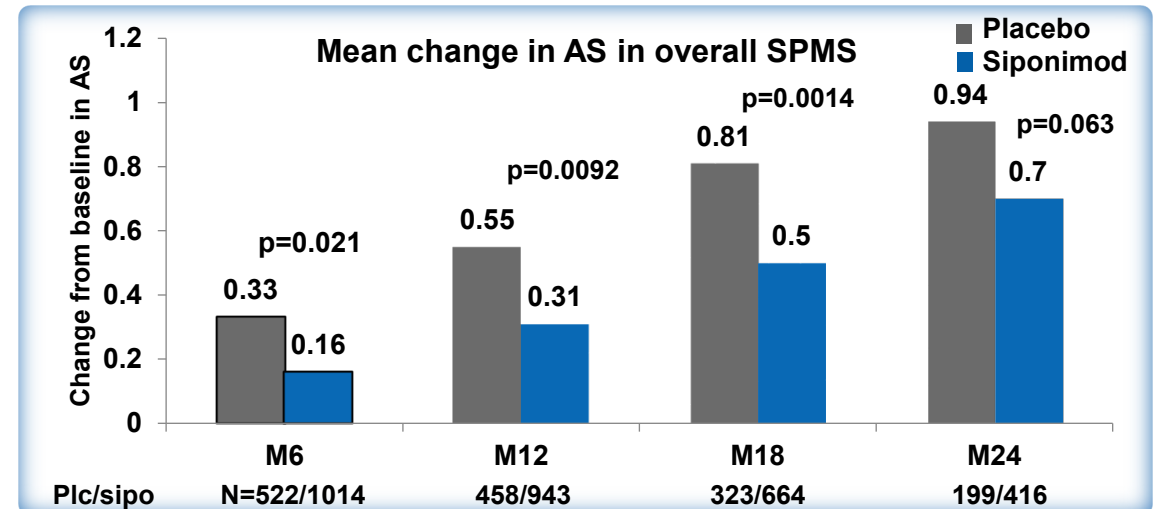
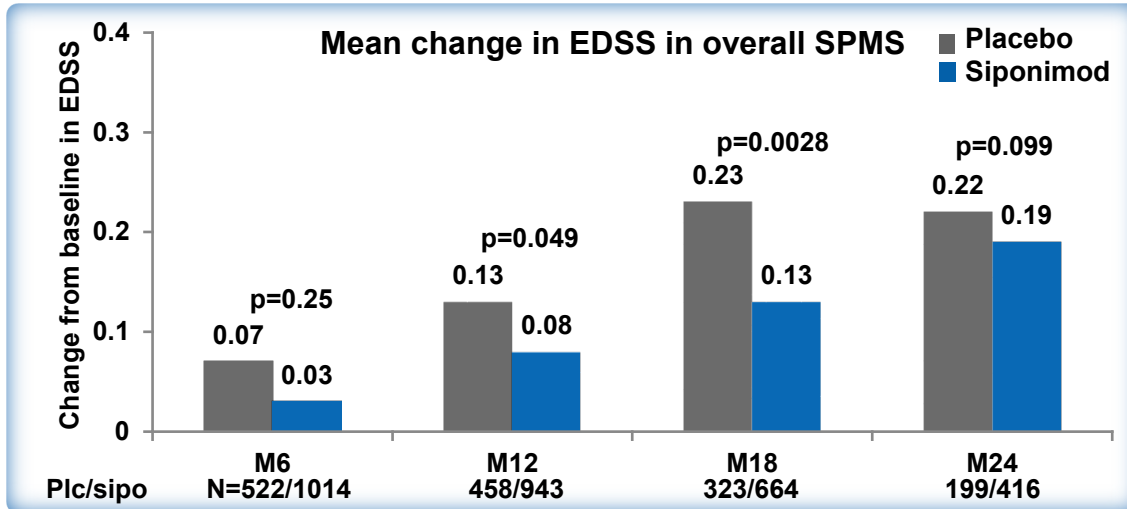
<sup>b</sup>patients with no relapse in prior 2 years and no gadolinium-enhancing lesions at baseline .

<sup>1</sup>Kappos L, et al., Lancet. 2018;391(10127):1263-1273;

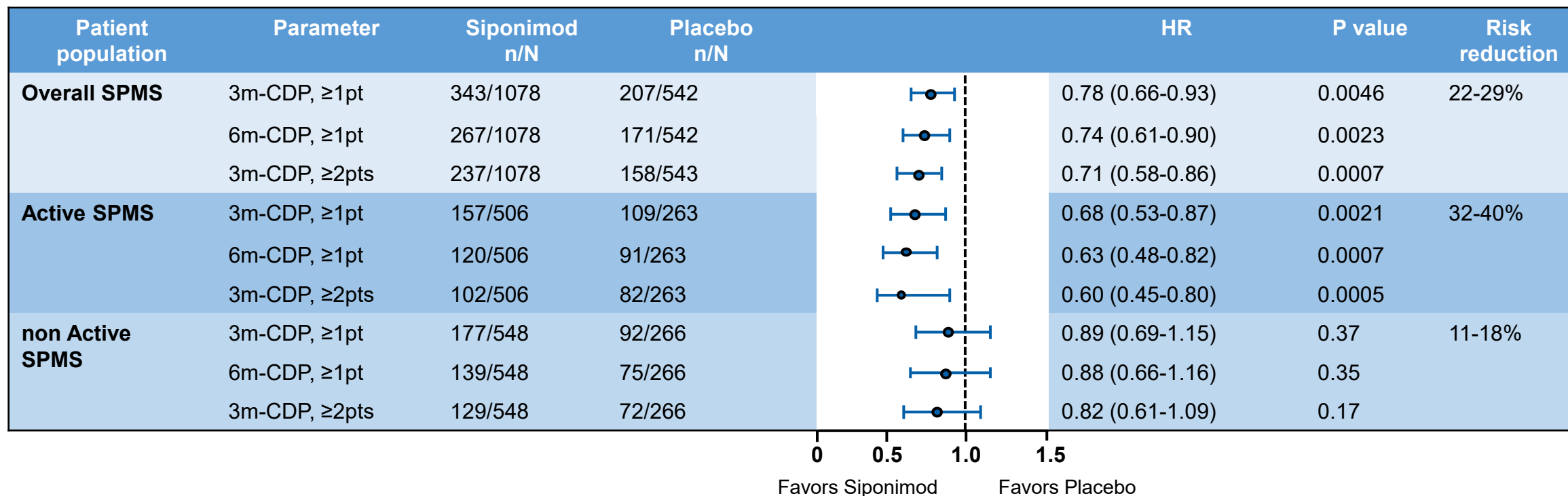
AS, ambulation score; EDSS, Expanded Disability Status Scale; SPMS, secondary progressive multiple sclerosis



# Results: Effect of siponimod on change in EDSS and AS from baseline in overall SPMS and in patients with active SPMS



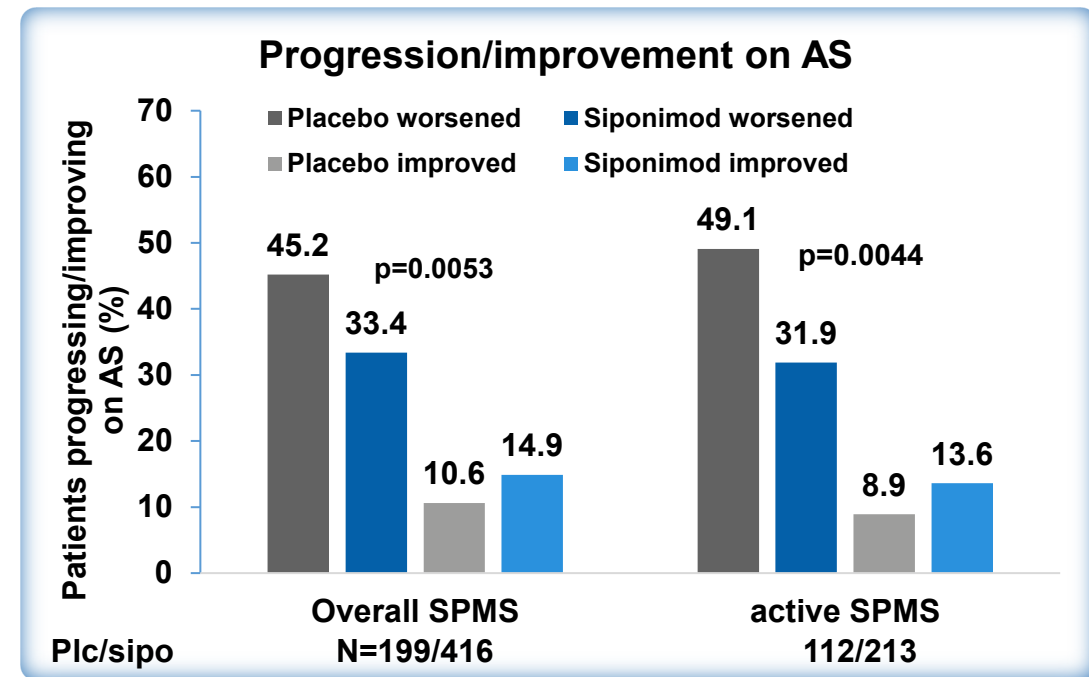
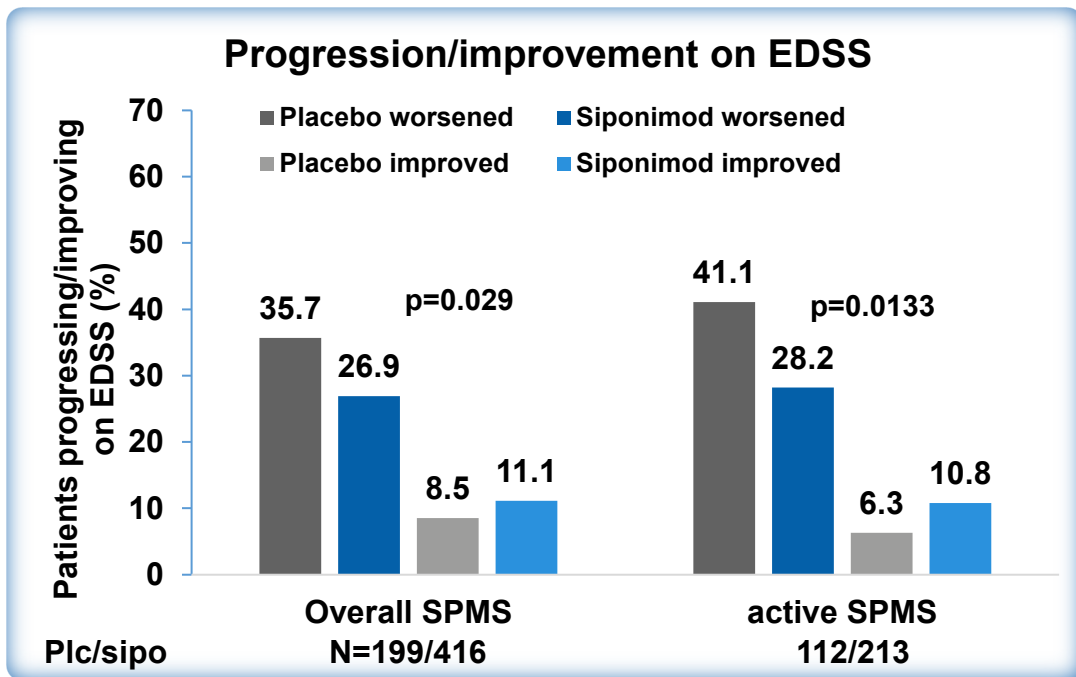
# Results: Effect of siponimod on time to confirmed disease progression as measured using the AS in patients with SPMS



- Siponimod significantly reduced the risk of confirmed progression on the AS in overall and in the active SPMS population; the reduction was more apparent with more stringent parameters



# Results: Effect of siponimod on proportion of patients with 6-m confirmed progression/improvement on EDSS and AS at 24 months



- Significantly fewer patients worsened, and more patients improved on siponimod compared to patients on placebo on both the EDSS and the AS in overall SPMS and in the active SPMS population
- In patients with non-active SPMS, trends favoring siponimod vs placebo were observed for both the EDSS and the AS with fewer patients worsening on siponimod (Neurostatus-EDSS 24.6% vs 29.4% and AS 34.4% vs 40%, p=ns)





- These findings corroborate the efficacy of siponimod on disability progression in patients with SPMS
- Siponimod had a more pronounced effect on both Neurostatus-eEDSS and AS scores in overall and active SPMS sub-group and with the more stringent endpoint definitions
  - In non-active SPMS patients, favorable non-significant trends were observed
- Significantly less patients worsened, and more patients improved on the EDSS and AS with siponimod vs placebo
- The ambulation score of the Neurostatus-eEDSS might provide complementary information on disability progression, especially in patients with higher EDSS scores (requiring walking aids)
- The Neurostatus-eEDSS is a standardized method to reduce inconsistencies and background noise of the neurological assessment and to reliably detect progression

