Early Reduction in Plasma Glial Fibrillary Acidic Protein Levels in Siponimod-Treated SPMS Patients (EXPAND) Is Associated With Reduced Risk of Disability Worsening

Jens Kuhle[1], Aleksandra Maleska Maceski[1], Rolf Meinert[2], Inga Ludwig[3], Thomas Hach[3], Goeril Karlsson[3], Ludwig Kappos[1], David Leppert[1]*, Harald Kropshofer[3]*

*contributed equally

ePoster presentation: P017

[1]Research Center for Clinical Neuroimmunology and Neuroscience Basel (RC2NB), Departments of Medicine, Clinical Research, Biomedicine and Biomedical Engineering, University Hospital and University of Basel, Basel, Switzerland; [2]DATAMAP GmbH, Freiburg, Germany; [3]Novartis Pharma AG, Basel, Switzerland

Poster Presentation at the ACTRIMS Forum 2021, February 25-27, 2021

Scan to download a copy of this presentation

Disclosures

Jens Kuhle's institution (University Hospital Basel) received and used exclusively for research support: consulting fees from Biogen, Novartis, Protagen AG, Roche, and Teva; speaker fees from the Swiss MS Society, Biogen, Novartis, Roche, and Genzyme; travel expenses from Merck Serono, Novartis, and Roche; grants from the ECTRIMS Research Fellowship Programme, University of Basel, Swiss MS Society, Swiss National Research Foundation (320030_160221), Bayer AG, Biogen, Genzyme, Merck, Novartis, and Roche.

David Leppert has been Therapeutic Area Head at Novartis, Neuroscience Development Unit, until January 2019. He is Chief Medical Officer of GeNeuro. He has received personal compensation for consulting and speaking, and travel reimbursement from Quanterix, Orion, Novartis, Roche and Sanofi.

Aleksandra Maleska Maceski has nothing to disclose.

Ludwig Kappos' institution (University Hospital Basel) received in the last 3 years and used exclusively for research support at the department: steering committee, advisory board, consultancy fees and support of educational activities from Actelion, Allergan, Almirall, Baxalta, Bayer, Biogen, Celgene/Receptos, CSL-Behring, Desitin, Excemed, Eisai, Genzyme, Japan Tobacco, Merck, Minoryx, Novartis, Pfizer, F. Hoffmann-La Roche Ltd, Sanofi Aventis, Santhera, and Teva; and license fees for Neurostatus-UHB products. The research of the MS center in Basel has been supported by grants from Bayer, Biogen, Novartis, the Swiss MS Society, the Swiss National Research Foundation, Inno-Suisse, the European Union, and Roche Research Foundations.

Rolf Meinert is an employee of DATAMAP GmbH.

Inga Ludwig, Thomas Hach, Goeril Karlsson, and **Harald Kropshofer** are employees of Novartis.

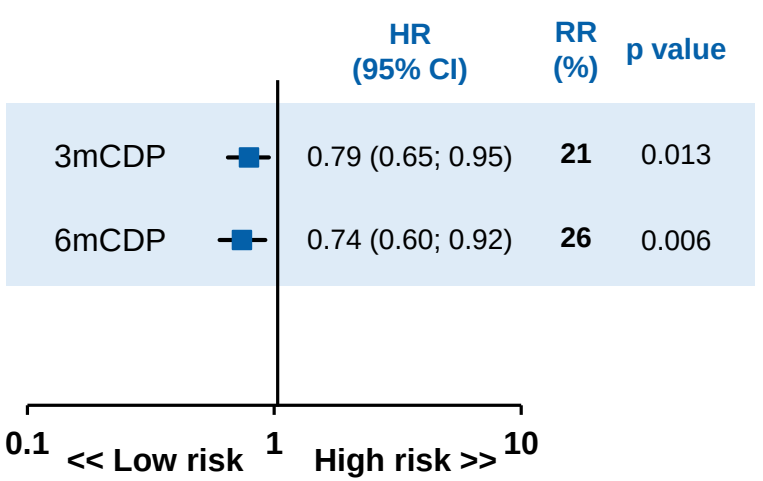
Funding source: This study is supported by Novartis Pharma AG, Basel, Switzerland.

Acknowledgments: Writing support was provided by **Saimithra Thammera** and **Uma Kundu** (employees of Novartis Healthcare Pvt. Ltd., Hyderabad, India). The final responsibility for the content lies with the authors.

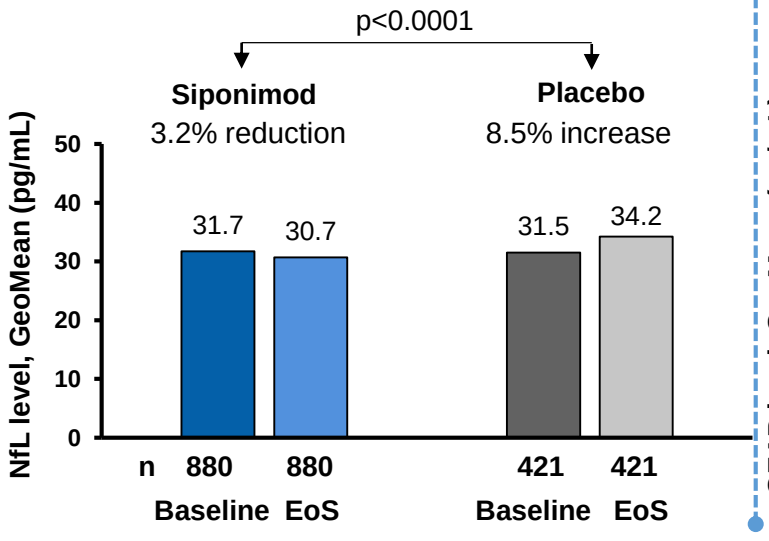
Background

- pNfL and pGFAP correlate with disease activity and have shown utility as markers of disability and treatment response in SPMS[1,2]
- In the EXPAND study, compared to placebo, siponimod significantly reduced:

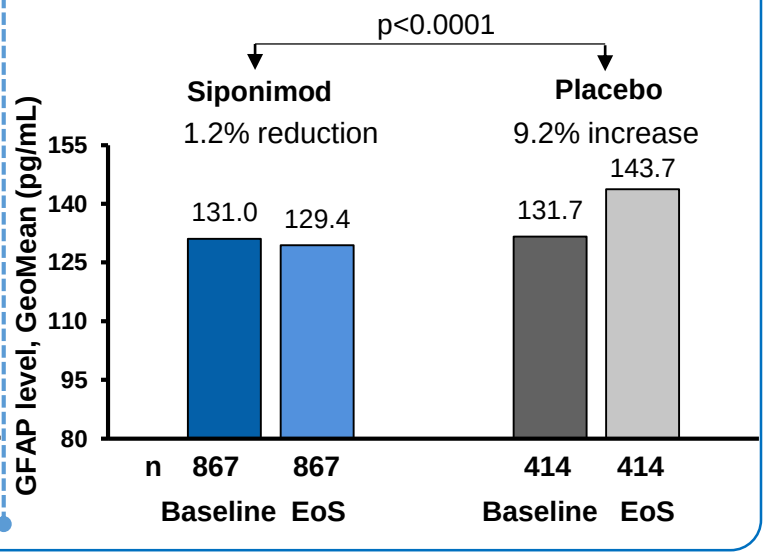
Time to 3mCDP and 6mCDP[3]



Change in NfL levels[1]



Change in GFAP levels[2]



- The predictive value of the change in these blood biomarker levels for disability worsening during the early stage of treatment has not been investigated

3m/6mCDP, 3-month/6-month confirmed disability progression; CI, confidence interval; EoS, end of study; GeoMean, geometric mean; pGFAP, plasma glial fibrillary acidic protein; HR, hazard ratio; pNfL, plasma neurofilament light chain; n, number of patients; RR, risk reduction; SPMS, secondary progressive multiple sclerosis

1. Kuhle J et al, et al. presented at *AAN* 2018. S8.006; 2. Kuhle J et al. Presented at *AAN* 2020. S10.006 3. Kappos L et al.. *Lancet* 2018; 391: 1263–73

Objective

To assess the predictive value of the change in pNfL and pGFAP levels from baseline to Month 3 for disability worsening in SPMS patients treated with siponimod or placebo

pGFAP, plasma glial fibrillary acidic protein; pNfL, plasma neurofilament light chain; SPMS, secondary progressive multiple sclerosis

Methods

A post hoc analysis from the Phase 3 EXPAND study in SPMS patients

pNfL and pGFAP assessments

- pNfL and pGFAP levels at baseline and Month 3 were quantified in EDTA plasma samples using Single Molecule Array technology
  - The impact of the change in pNfL levels on clinical disability outcomes was analyzed in patients with baseline pNfL >20 pg/mL (>15% quantile; independent from pGFAP)
  - The impact of the change in pGFAP levels on clinical disability outcomes was analyzed in patients with baseline pGFAP >75 pg/mL (>10% quantile; independent from pNfL)

Outcomes (data from the EXPAND core phase)

- The relationship between changes in pNfL and pGFAP levels from baseline to Month 3 (increase [≥0] vs decrease [<0]) and the below outcomes measured from Month 3 to EoS was assessed
  - Time to 3mCDW
  - Time to 1-point sustained EDSS worsening
  - Time to sustained EDSS 7.0

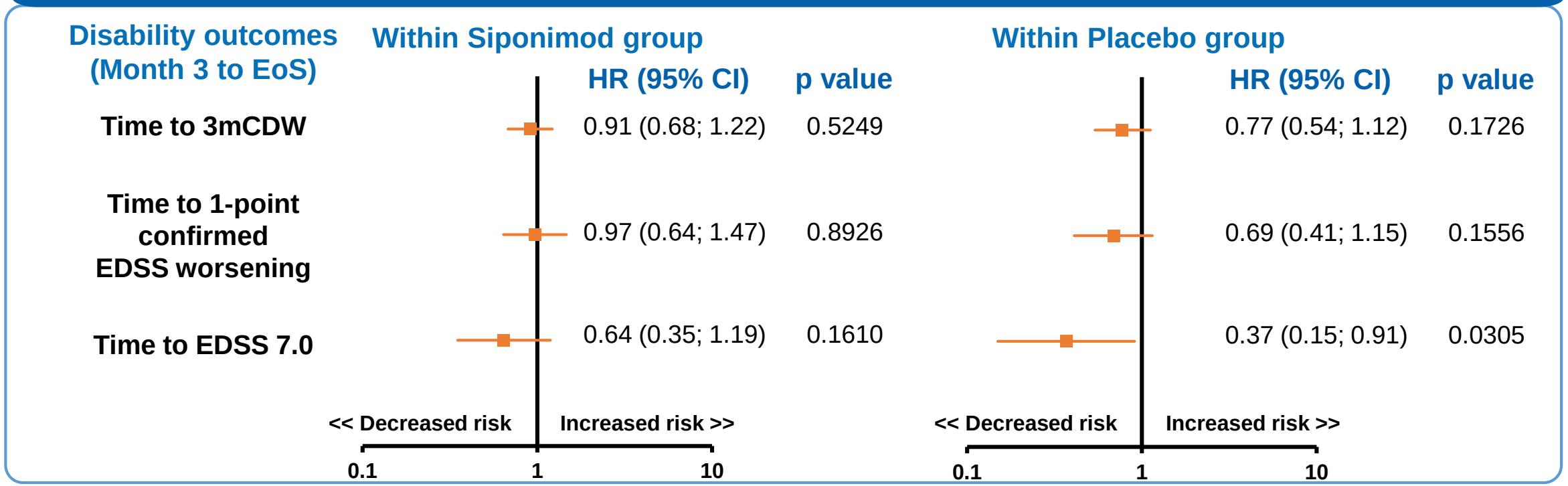
Statistical analysis

- Cox regression models adjusted for age, gender, disease duration at baseline and relapses in the 24 months before study initiation, and EDSS score at Month 3
- In order to account for biomarker changes occurring under different treatment conditions, analyses were conducted separately for the siponimod and placebo groups

3mCDW, 3-month confirmed disability worsening; EDSS, Expanded Disability Status Scale; EDTA, ethylenediaminetetraacetic acid; EoS, end of the study; pGFAP, glial fibrillary acidic protein; pNfL, plasma neurofilament light chain; SPMS, secondary progressive multiple sclerosis

Association Between the Change in pNfL and Disability Outcomes

Risk of disability worsening: Reduction versus increase or no change in pNfL between baseline and Month 3



The decrease in pNfL from baseline to Month 3 under siponimod and placebo treatment showed similar trends in reducing the disability worsening from Month 3 to EoS in both the groups. This indicates that the lower the pNfL level, the lower the risk of disability worsening.

3mCDW, 3-month confirmed disability worsening; CI, confidence interval; EDSS, Expanded Disability Status Scale; EoS, end of study; HR, hazard ratio; pNfL, plasma neurofilament light chain

Association Between the Change in pNfL and Disability Outcomes

	Disability outcome (Month 3 to EoS)	<0 change[a] n/N (%)	≥0 change[a] n/N (%)	HR (95% CI)	p value	Difference in risk (%)
Siponimod	Time to 3mCDW	91/402 (23%)	86/351 (25%)	0.91 (0.68; 1.22)	0.5249	−9
	Time to 1-point confirmed EDSS worsening	48/402 (12%)	44/351 (13%)	0.97 (0.64; 1.47)	0.8926	−3
	Time to EDSS 7.0	19/397 (5%)	23/342 (7%)	0.64 (0.35; 1.19)	0.1610	−36
Placebo	Time to 3mCDW	56/191 (29%)	60/174 (35%)	0.77 (0.54; 1.12)	0.1726	−23
	Time to 1-point confirmed EDSS worsening	27/191 (14%)	32/174 (18%)	0.69 (0.41; 1.15)	0.1556	−31
	Time to EDSS 7.0	8/190 (4%)	18/173 (10%)	0.37 (0.15; 0.91)	0.0305	−63

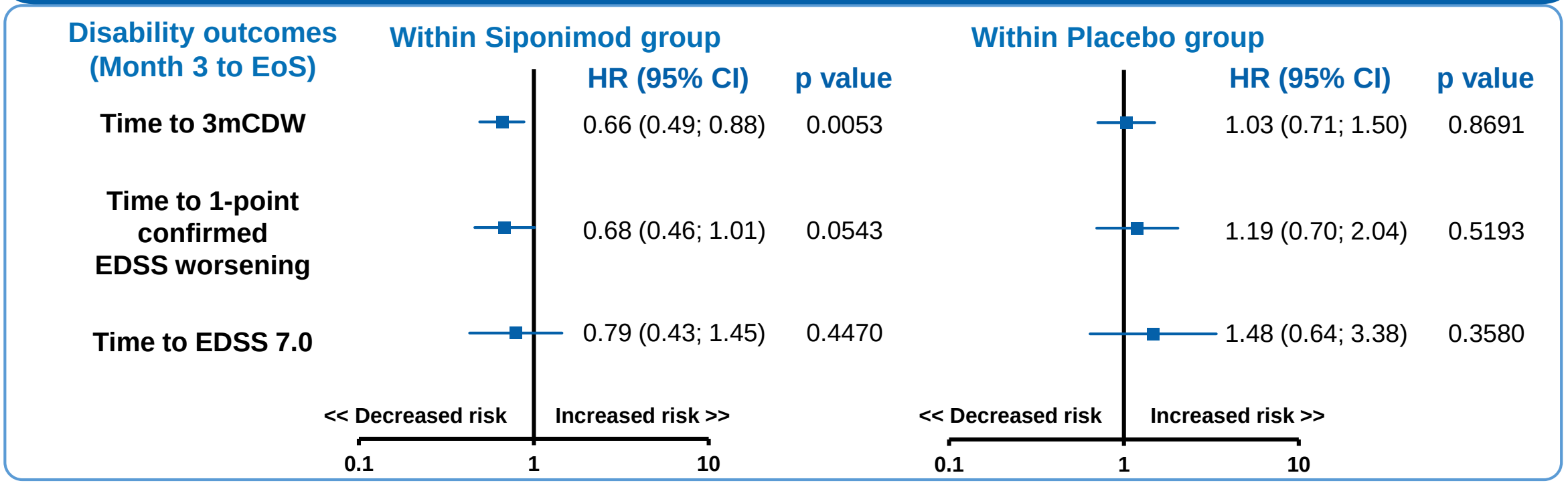
[a]Change from baseline to Month 3 measured in patients with baseline pNfL >20 pg/mL

Cox regression models adjusted for age, gender, disease duration at baseline and relapses in the 24 months before study initiation, and EDSS score at Month 3

3mCDW, 3-month confirmed disability worsening; CI, confidence interval; EDSS, Expanded Disability Status Scale; EoS, end of study; HR, hazard ratio; n, number of patients with an event; N, number of patients included in the analysis; pNfL, plasma neurofilament light chain

Association Between the Change in pGFAP and Disability Outcomes

Risk of disability worsening: Reduction versus increase or no change in pGFAP between baseline and Month 3



Reduction in pGFAP from baseline to Month 3 under siponimod treatment indicated a reduced risk of disability worsening from Month 3 to EoS while on siponimod treatment; however, a reduction in pGFAP under placebo did not indicate a subsequent reduced risk of worsening in the placebo group

3mCDW, 3-month confirmed disability worsening; CI, confidence interval; EDSS, Expanded Disability Status Scale; EoS, end of study; HR, hazard ratio; pGFAP, plasma glial fibrillary acidic protein

Association Between the Change in pGFAP and Disability Outcomes

	Disability outcome (Month 3 to EoS)	<0 change[a] n/N (%)	≥0 change[a] n/N (%)	HR (95% CI)	p value	Difference in risk (%)
Siponimod	Time to 3mCDW	81/427 (19%)	100/367 (27%)	0.66 (0.49; 0.88)	0.0053	−34
	Time to 1-point confirmed EDSS worsening	49/427 (12%)	51/367 (14%)	0.68 (0.46; 1.01)	0.0543	−32
	Time to EDSS 7.0	19/423 (5%)	24/358 (7%)	0.79 (0.43; 1.45)	0.4470	−21
Placebo	Time to 3mCDW	69/219 (32%)	49/168 (29%)	1.03 (0.71; 1.50)	0.8691	3
	Time to 1-point confirmed EDSS worsening	40/219 (18%)	22/168 (13%)	1.19 (0.70; 2.04)	0.5193	19
	Time to EDSS 7.0	20/218 (9%)	9/167 (5%)	1.48 (0.64; 3.38)	0.3580	48

[a]Change from baseline to Month 3 measured in patients with baseline pGFAP >75 pg/mL

Cox regression models adjusted for age, gender, disease duration at baseline and relapses in the 24 months before study initiation, and EDSS score at Month 3

3mCDW, 3-month confirmed disability worsening; CI, confidence interval; EDSS, Expanded Disability Status Scale; EoS, end of study; HR, hazard ratio; n, number of patients with an event; N, number of patients included in the analysis; pGFAP, plasma glial fibrillary acidic protein

Conclusions

- This is the first study that supports an association of the early lowering in pGFAP levels and a long-term reduced risk of disability worsening in patients with SPMS under disease-modifying treatment
- A decrease in pNfL was associated with an only slightly decreased risk of disability worsening, irrespective of the treatment received
- GFAP is apparently sensitive to the treatment received and may therefore qualify not only as a disease marker that is prognostic of disability worsening, but also as a marker of treatment response
- This is a post hoc analysis and the study may not be powered to show clinically relevant effects with statistical significance. Additional evidence from future studies is needed to confirm these findings

GFAP, glial fibriallry acidic protein; NfL, neurofilament light chain; pGFAP, plasma glial fibrillary acidic protein; pNfL, plasma neurofilament light chain; SPMS, secondary progressive multiple sclerosis