EPR3098

Effect of Siponimod on Grey Matter Atrophy in Patients With Secondary Progressive Multiple Sclerosis: Subgroup Analyses From the EXPAND Study

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ePresentation Session: MS and Related Disorders
May 25, 2020

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Disclosures

Robert J. Fox has received compensation for serving as a consultant or speaker from Allozyne, Avanir, Biogen, Novartis, Questcor and Teva Pharmaceutical Industries. He, or the institution he works for, has received research support from Novartis.

Douglas L. Arnold has received honoraria from Acorda, Biogen Idec, Genentech, Genzyme, Novartis, F. Hoffmann-La Roche and Sanofi-Aventis; research support from Novartis and Biogen; and has an equity interest in NeuroRx Research, which performed the MRI analysis for the trial.

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 and 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.

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.

Ralf Gold has received compensation for serving as a consultant or speaker from Bayer HealthCare, Biogen, Merck, Novartis and Teva. He, or the institution he works for, has received research support from Bayer HealthCare, Biogen, Merck, Novartis and Teva. He has also received honoraria as a Journal Editor from SAGE and Thieme Verlag.

Ralph H.B. Benedict has received fees from Acorda Therapeutics, Biogen, EMD Serono, Mallinckrodt, National Multiple Sclerosis Society, Novartis Pharmaceuticals Corporation, Roche-Genentech and Sanofi-Genzyme.

Ludwig Kappos' institution (University Hospital Basel) has received the following exclusively for research support: steering committee, advisory board and consultancy fees (Actelion, Addex, Bayer HealthCare, Biogen Idec, Biotica, Genzyme, Lilly, Merck, Mitsubishi, Novartis, Ono Pharma, Pfizer, Receptos, Sanofi, Santhera, Siemens, Teva, UCB and Xenoport); speaker fees (Bayer HealthCare, Biogen Idec, Merck, Novartis, Sanofi and Teva); support for educational activities (Bayer HealthCare, Biogen, CSL Behring, Genzyme, Merck, Novartis, Sanofi and Teva); license fees for Neurostatus products; and grants (Bayer HealthCare, Biogen Idec, European Union, Innoswiss, Merck, Novartis, Roche Research Foundation, Swiss MS Society and Swiss National Research Foundation).

Patrick Vermersch has received honoraria and consulting fees from Biogen, Sanofi, Teva, Novartis, Merck and Almirall, and research support from Biogen, Sanofi, Bayer and Merck.

Daniela Piani Meier, **Sophie Arnould**, **Shannon Ritter**, **Frank Dahlke** and **Goeril Karlsson** are employees of Novartis.

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

Acknowledgement: Medical writing support was provided by **Richa Chhabra** (employee of Novartis Healthcare Pvt. Ltd., Hyderabad, India). The final responsibility for the content lies with the authors.

Background: Clinical Relevance of Grey Matter Atrophy

- Cortical grey matter (cGM) and thalamic volume loss is associated with long-term disability accumulation and cognitive decline[1-4]
- Preclinical studies suggest that siponimod effectively impacts neurodegenerative processes in the CNS[5,6]
- In the EXPAND overall population, siponimod significantly reduced both cGM and thalamic volume loss in SPMS patients[7], supporting its clinical effects on disability progression and cognitive processing speed

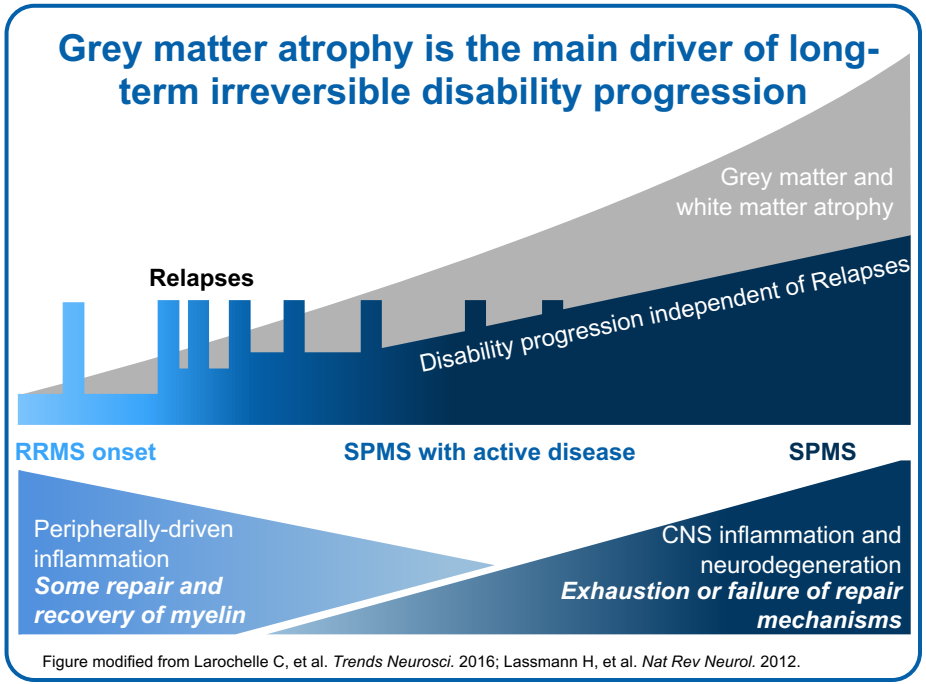


Figure modified from Larochelle C, et al. *Trends Neurosci.* 2016; Lassmann H, et al. *Nat Rev Neurol.* 2012.

CNS, central nervous system; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis

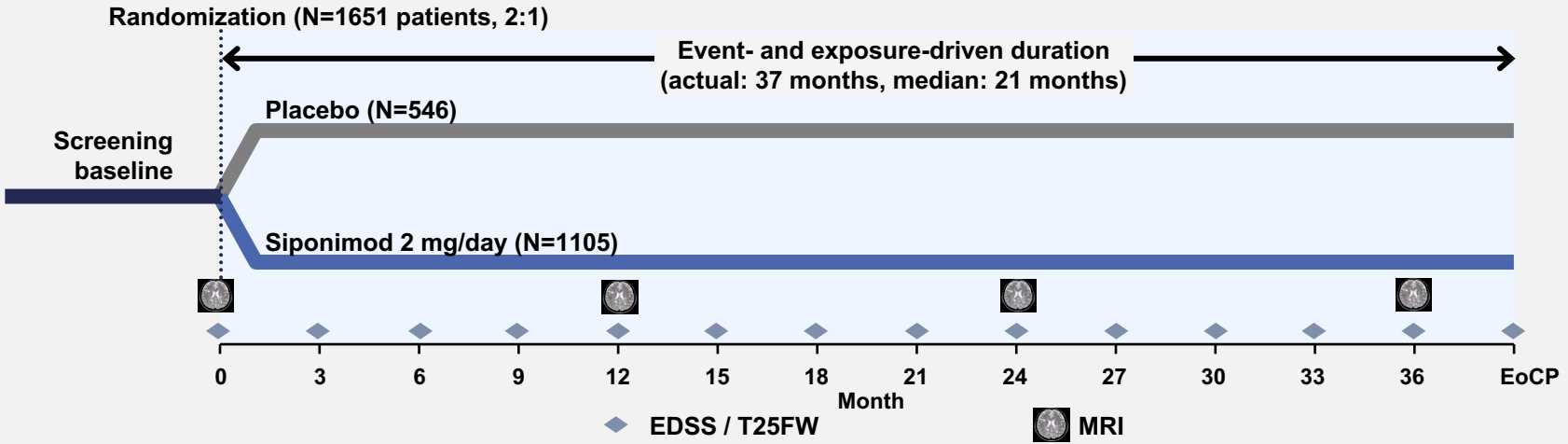
1. Eshaghi A, et al. *Ann Neurol*. 2018;83:210–222; 2. Scalfari A, et al. *Neurology*. 2018;90:e2107–e2118; 3. Fisniku LK, et al. *Ann Neurol*. 2008;64(3):247–254; 4. Eijlers AJC, et al. *Brain*. 2018;141:2605–2618; 5. Gentile A, et al. *J Neuroinflammation*. 2016;13:207; 6. Behrangi N, et al. *Cells*. 2019;8. pii: E24; 7. Arnold DL, et al. Poster presented at *ECTRIMS* 2019. P382.

Objective and Study Design

Objective

To investigate the effect of siponimod versus placebo in reducing cGM and thalamic atrophy in subgroups of SPMS patients from the EXPAND study

Randomised, double-blind, placebo-controlled, event- and exposure-driven study



Patients who had 6-month CDP during the treatment epoch were provided with options that included starting treatment with open-label siponimod as rescue medication.
cGM, cortical grey matter; EDSS, Expanded Disability Status Scale; EoCP, end of core phase; MRI, magnetic resonance imaging; N, total number of patients; SPMS, secondary progressive multiple sclerosis; T25FW, Timed 25-Foot Walk

Methods and Subgroups

- Post-hoc analyses included the PPS (N=1560; excluding major protocol deviations and data after the treatment switch) and the FAS (N=1645)
- Percent volume changes in cGM and the thalamus (baseline to M12 and M24 respectively) were assessed in:

Subgroups by disease history and severity

- Age (≤45/>45 years)
- Disease duration (≤15/>15 years)
- EDSS score (<6.0/≥6.0)
- SDMT score (≤43/>43)

Subgroups by inflammatory disease activity

- Active/non-active SPMS*
- With/without relapses in the 2 years prior to screening
- With/without Gd+ lesions

Statistical method

- Treatment effects were analysed in both the FAS and the PPS. Here, we present the data for the PPS only
- Treatment effects were determined using a Mixed Model for Repeated Measures[#]
  - No adjustment for multiplicity was made

*Patients with active disease were defined as those with at least one relapse in the prior 2 years and/or at least one Gd+ lesion at baseline, while non-active patients were defined as those with no relapses in the prior 2 years and no Gd+ lesions at baseline.

[#]Adjusted for treatment, visit, NBV, number of baseline Gd+ T1 lesions, baseline T2 lesion volume, and the interaction of visit by treatment and visit by baseline brain volume.

cGM, cortical grey matter; EDSS, Expanded Disability Status Scale; FAS, full analysis set; Gd+, gadolinium-enhancing; M, month; MMRM, mixed-model for repeated measures; NBV, normalised brain volume; PPS, per protocol set; SDMT, Symbol Digit Modalities Test; SPMS, secondary progressive multiple sclerosis

Effect of Siponimod on cGM Atrophy at M24* vs Placebo by Subgroups (PPS)

Subgroups	Placebo	Siponimod	n/n (siponimod/ placebo)	Percentage reduction vs placebo (p value)
Age ≤45 years	-0.94	-0.3	246/120	69% (p<0.0001)
Age >45 years	-1.08	-0.45	446/217	57% (p<0.0001)
Disease duration ≤15 years	-1.05	-0.36	318/171	66% (p<0.0001)
Disease duration >15 years	-1.04	-0.42	374/165	60% (p<0.0001)
EDSS <6.0	-1.04	-0.37	319/165	64% (p<0.0001)
EDSS ≥6.0	-1.04	-0.42	373/172	60% (p<0.0001)
SDMT >43	-0.98	-0.23	299/159	76% (p<0.0001)
SDMT ≤43	-1.11	-0.51	387/176	54% (p<0.0001)
Non-active SPMS	-0.94	-0.27	344/167	72% (p<0.0001)
Active SPMS	-1.14	-0.5	347/169	55% (p<0.0001)
Without superimposed relapses	-0.94	-0.28	431/205	70% (p<0.0001)
With superimposed relapses	-1.17	-0.57	259/131	51% (p<0.0001)
Without Gd+ lesions	-1.01	-0.34	530/268	66% (p<0.0001)
With Gd+ lesions	-1.12	-0.58	162/69	47% (p=0.0089)

Percentage change in cGM volume from baseline to M24

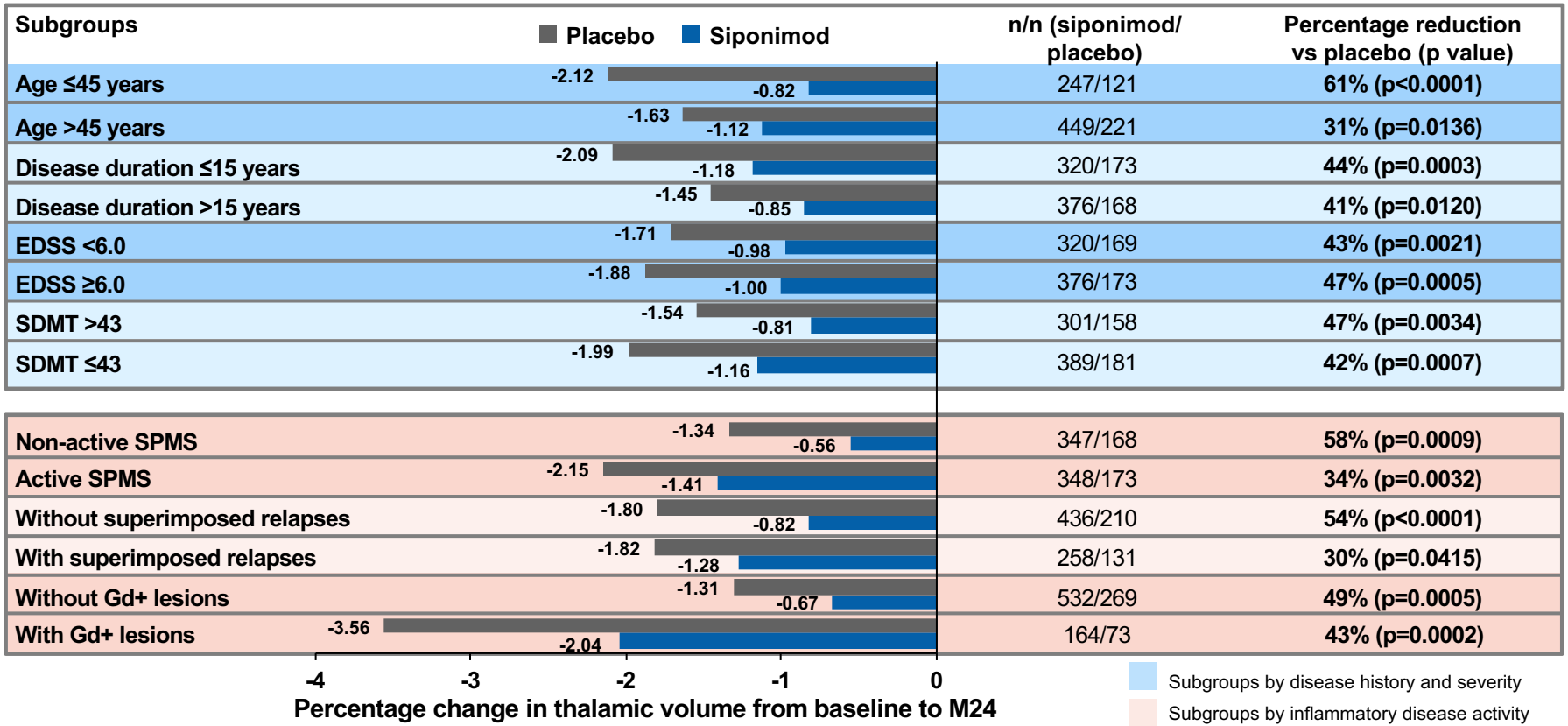
Subgroups by disease history and severity

Subgroups by inflammatory disease activity

*At M12, percentage reduction ranged from 84% to 118% (p<0.0001 for all).

cGM, cortical grey matter; EDSS, Expanded Disability Status Scale; Gd+, gadolinium-enhancing; M, month; PPS, per protocol set; SDMT, Symbol Digit Modalities Test;

Effect of Siponimod on Thalamic Atrophy at M24* vs Placebo by Subgroups (PPS)



*At M12, percentage reduction ranged from 33% to 68% (p<0.05 for all except disease duration >15 years).
EDSS, Expanded Disability Status Scale; Gd+, gadolinium-enhancing; M, month; PPS, per protocol set; SDMT, Symbol Digit Modalities Test

Summary

- Siponimod significantly reduced cGM atrophy by 47-76% and thalamic atrophy by 30-61% over 24 months across the patient subgroups
  - The beneficial effect was consistently observed independent of age, disease duration, disease activity and severity
- A reduction of grey matter atrophy might positively impact long-term clinical outcomes, including disability progression and cognitive decline[1-6]
- The data are in line with siponimod preclinical studies[7,8], showing beneficial direct CNS effects, including promotion of remyelination and corroborate the favourable effects of siponimod on MTR measures (For MTR results from the EXPAND study, please refer to EPR1147)

cGM, cortical grey matter; CNS, central nervous system; MTR, magnetization transfer ratio

1. Eshaghi A, et al. *Ann Neurol*. 2018;83:210–222; 2. Rocca MA, et al. *Radiology*. 2010;257:463–469; 3. Schoonheim MM, et al. *Neurology*. 2015;84:776–783; 4. Scalfari A, et al. *Neurology*. 2018;90:e2107-e2118; 5. Fisniku LK, et al. *Ann Neurol*. 2008;64(3):247-54; 6. Eijlers AJC, et al. *Brain*. 2018;141:2605-2618; 7. Martin E et al. *ECTRIMS 2019*; P1376; 8. Mannioui A, et al. *Mult Scler.* 2018; 24(11):1421–1432.

Thank you