EPR2118

Siponimod Slows Physical Disability Progression and Decline in Cognitive Processing Speed in SPMS Patients with Active Disease: A Post Hoc Analysis of the EXPAND Study

Ralf Gold[1], Ludwig Kappos[2], Ralph H.B. Benedict[3], Amit Bar-Or[4], Patrick Vermersch[5], Gavin Giovannoni[6], Robert J. Fox[7], Thomas Hach[8], Shannon Ritter[9], Nicolas Rouyrre[8], Goeril Karlsson[8], Bruce A.C. Cree[10]

ePresentation Session: MS and Related Disorders
May 24, 2020

[1]Department of Neurology, St. Josef-Hospital/Ruhr-University Bochum, Bochum, Germany; [2]Neurologic Clinic and Policlinic, Departments of Medicine, Clinical Research, Biomedicine and Biomedical Engineering, University Hospital and University of Basel, Basel, Switzerland; [3]Department of Neurology, University at Buffalo, Buffalo, NY, USA; [4]Center for Neuroinflammation and Experimental Therapeutics and Department of Neurology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA; [5]Univ. Lille, INSERMU995, CHU Lille, FHU Imminent, F-59000 Lille, France; [6]Blizard Institute, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London, United Kingdom; [7]Mellen Center for Treatment and Research in Multiple Sclerosis, Neurological Institute, Cleveland Clinic, Cleveland, OH, USA; [8]Novartis Pharma AG, Basel, Switzerland; [9]Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA; [10]Department of Neurology, UCSF Weill Institute for Neurosciences, University of California San Francisco, San Francisco, CA, USA

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Disclosures

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

Ludwig Kapposinstitution (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).

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

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..

Patrick Vermersch has received honoraria and consulting fees from Biogen Idec, Genzyme-Sanofi, Bayer, Novartis, Merck Serono, GlaxoSmithKline and Almirall, and research support from Biogen Idec, Genzyme-Sanofi, Bayer and Merck Serono.

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, Genzyme-Sanofi, 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).

Robert J. Fox has received personal consulting fees from Actelion, Biogen, Celgene, EMD Serono, Genentech, Immunic, Novartis and Teva. He has served on advisory committees for Actelion, Biogen, Immunic and Novartis, and received clinical trial contract and research grant funding from Biogen and Novartis.

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

Thomas Hach, **Shannon Ritter**, **Nicolas Rouyrre**, 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 **Sreelatha Komatireddy** and **Anuja Shah** (employees of Novartis Healthcare Pvt. Ltd., Hyderabad, India). The final responsibility for the content lies with the authors.

Background

- In the core part of the Phase 3 EXPAND study, siponimod significantly reduced the relative risk of 3-month CDP by 21% and 6-month CDP by 26% compared with placebo and showed clinically meaningful benefits in cognitive processing speed[1,2]
- Furthermore, in SPMS patients with active disease[a], siponimod significantly reduced clinical and MRI outcomes versus placebo[3]:
  - 3-month CDP by 31% and 6-month CDP by 37%
  - Annualised relapse rate by 46%
  - Risk of cumulative number of T1 Gd+ lesions by 85%
  - Number of new/enlarging T2 lesions by 80%

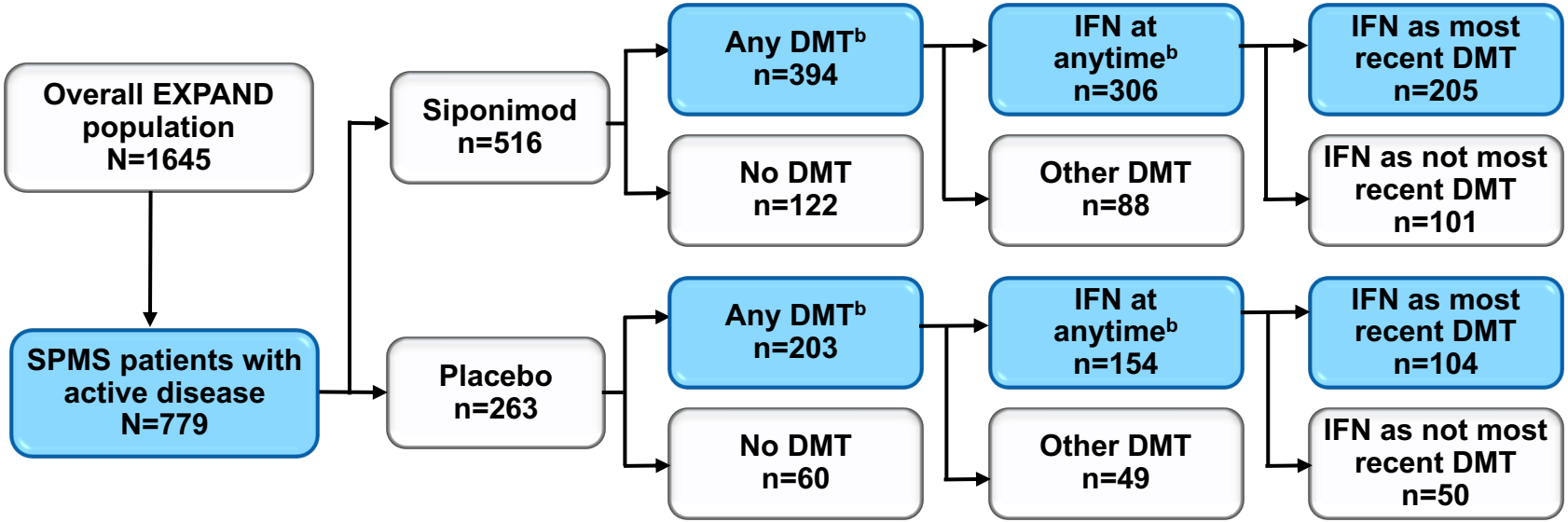
Objective: To assess the efficacy of siponimod on disability progression and cognitive processing speed in SPMS patients with active disease

[a]Defined as the presence of relapses in the 2 years before screening and/or ≥1 T1 Gd+ lesion at baseline. CDP, confirmed disability progression; Gd+, gadolinium-enhancing; MRI, magnetic resonance imaging; SDMT, Symbol Digit Modalities Test; SPMS, secondary progressive multiple sclerosis

[1]Kappos L, et al. *Lancet* 2018;391:1263-1273; [2]Benedict R, et al. Presented at AAN 2018. S44.004.; [3]Gold R, et al. Presented at ECTRIMS 2019. P750.

Patient Population

This post-hoc analysis included SPMS patients with active disease[a] and subgroups of patients with active disease, defined based on previous DMT use at baseline



Patient groups highlighted in blue box are included in the analysis

[a]defined as patients with relapses in the 2 years before screening and/or ≥1 Gd+ T1 lesion at baseline; [b]patients those who received and stopped IFN/MS-DMT prior to first dose of study treatment

DMT, disease-modifying therapy; Gd+, gadolinium-enhancing; IFN, interferon; SPMS, secondary progressive multiple sclerosis

Study Outcomes and Statistical Analysis

Outcomes/patients	Statistical method
In all SPMS patients with active disease	
• **Time to 3mCDP and 6mCDP**	• Using a Cox proportional hazards model with treatment, country/region, baseline EDSS and SPMS group (with/without superimposed relapses, baseline definition) as covariates
• **Sustained[a] worsening/improvement in cognitive processing speed** *(clinically meaningful change [≥4 points] on the SDMT score)*	• Using a Cox proportional hazards model with treatment, country, baseline EDSS, baseline SDMT-Oral score and SPMS group (with/without superimposed relapses, baseline definition) as covariates
In subgroups of patients with active disease	
• **Time to 6mCDP**	• Cox proportional hazards model with treatment and baseline EDSS as covariates

[a]sustained on all available assessments after the assessment of a negative/positive response
CDP, confirmed disability progression; EDSS, Expanded Disability Status Scale; Gd+, gadolinium-enhancing; SDMT, Symbol Digit Modalities Test; SPMS, secondary progressive multiple sclerosis

Baseline Demographics and Patient Characteristics

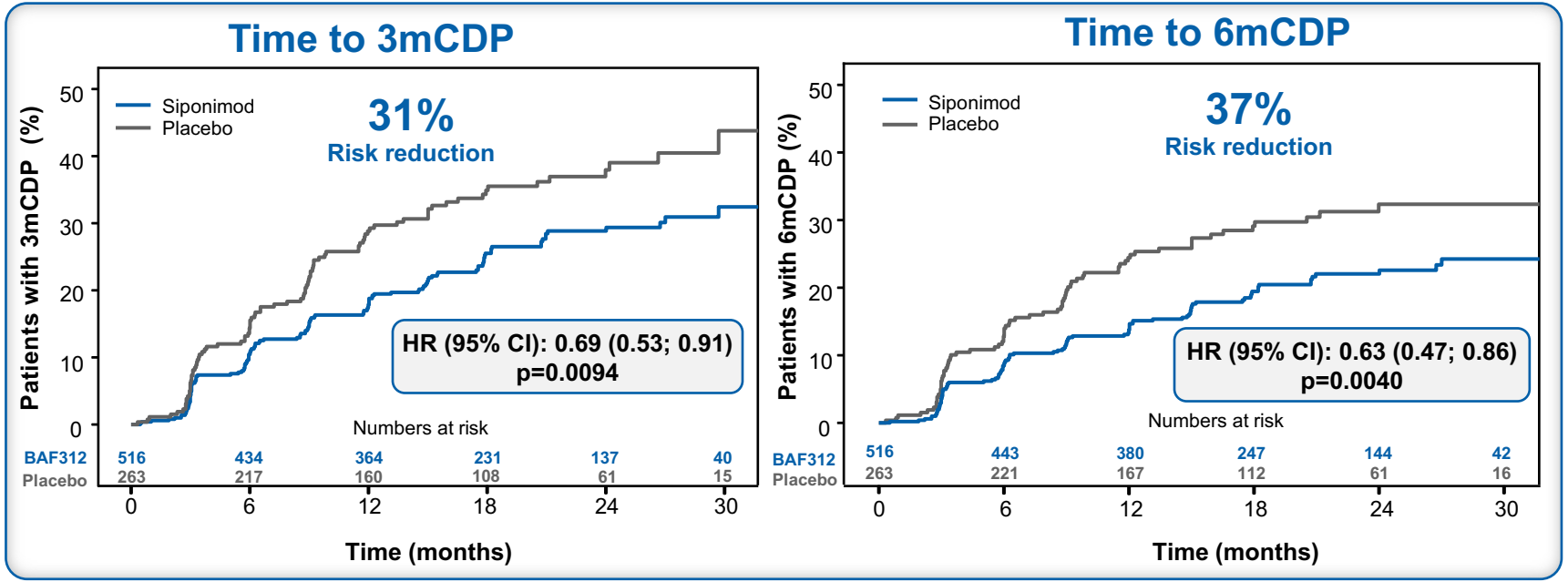
	All SPMS patients with active disease		Overall EXPAND population (N=1645)
	Siponimod n=516	Placebo n=263	
Age, years	46.2±8.1	47.2±8.5	48±7.9
Women, n (%)	331 (64.1)	166 (63.1)	987 (60.0)
Duration of MS since first symptom, years	15.6±7.9	15.5±8.2	16.8±8.3
Time since conversion to SPMS, years	3.2±3.3	3.1±3.2	3.8±3.5
EDSS, median (range)	6.0 (2.0–7.0)	6.0 (2.5–6.5)	6.0 (2.0–7.0)
SDMT	38.1±14.0	38.6±13.2	39.1±13.8
Patients with relapses in the previous 2 years before screening, n (%)	388 (75.2)	202 (76.8)	590 (36.0)
Proportion of patients with Gd+ T1 lesions, n (%)	236 (46.7)	114 (44.2)	351 (21.3)
T2 lesion volume, cm^3, median (range)	12.0 (0.0–116.6)	12.7 (0.0–103.6)	10.0 (0.0–116.6)
Normalised brain volume, cm^3, median (range)	1417.7 (1171–1723)	1417.8 (1228–1679)	1422.3 (1136–1723)

SPMS patients with active disease had more relapses and more MRI activities, as expected, compared with the overall EXPAND population. Otherwise the patient characteristics were similar

Data are presented as mean (SD), unless stated otherwise; EDSS, Expanded Disability Status Scale; Gd+, gadolinium-enhancing; MS, multiple sclerosis; SD, standard deviation; SDMT, Symbol Digit Modalities Test; SPMS, secondary progressive multiple sclerosis

Effect of Siponimod on Time to 3mCDP and 6mCDP

All SPMS patients with active disease



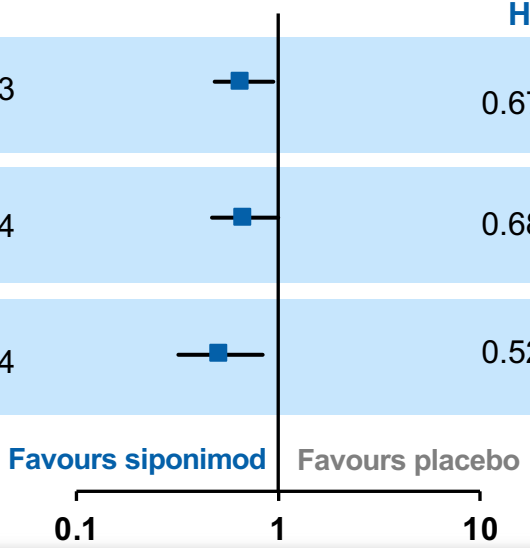
Siponimod significantly reduced the risk of 3mCDP by 31% and 6mCDP by 37% versus placebo in all active patients

CDP, confirmed disability progression; CI, confidence interval; HR, hazard ratio; SPMS, secondary progressive multiple sclerosis

Effect of Siponimod on 6mCDP

Subgroups of patients with active disease based on previous DMT use at baseline

	Siponimod n/N	Placebo n/N	HR (95% CI)	p value	Risk reduction
Any DMT	80/394	59/203	0.67 (0.48; 0.94)	0.0203	**33%**
Interferon at anytime	65/306	46/154	0.68 (0.47; 1.00)	0.0496	**32%**
Interferon as recent DMT	36/205	33/104	0.52 (0.32; 0.83)	0.0063	**48%**



Siponimod significantly reduced the risk of 6mCDP in all subgroups of patients regardless of previous treatment and this was consistent in all SPMS patients with active disease

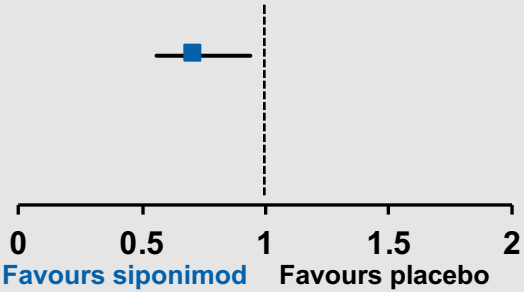
CDP, confirmed disability progression; CI, confidence interval; DMT, disease-modifying therapy; HR, hazard ratio; SPMS, secondary progressive multiple sclerosis

Effect of Siponimod on Cognitive Processing Speed

All SPMS patients with active disease

Sustained[a] worsening

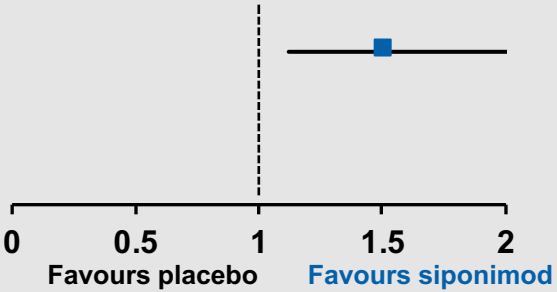
HR (95% CI)	p value	Risk reduction
0.72 (0.56; 0.94)	0.0166	**28%**



Siponimod	Placebo
n/N: 140/512	n/N: 100/262

Sustained[a] improvement

HR (95% CI)	p value	Risk improvement
1.51 (1.12; 2.04)	0.0070	**51%**



Siponimod	Placebo
n/N: 175/512	n/N: 60/262

Siponimod reduced the risk of sustained worsening in cognitive processing speed by 28% and improved the chance of sustained improvement by 51% versus placebo

[a]sustained on all available assessments after the assessment of a negative/positive response; Only patients with non-missing covariates are included in the model; CI, confidence interval; HR, hazard ratio; SPMS, secondary progressive multiple sclerosis

Conclusions

- Siponimod significantly and delayed disability progression versus placebo in SPMS patients with active disease,
  - Reduced the relative risk of 3-month CDP (31%)
  - Reduced the relative risk of 6-month CDP (37%)
  - Relative risk reduction of 6-month CDP was consistent across subgroups of patients with active disease based on previous DMT use (32%-48%)
- Siponimod showed significant benefits in cognitive processing speed versus placebo in SPMS patients with active disease
  - Reduced the risk of sustained worsening (by 28%)
  - Improved the chance of sustained improvement (by 51%)

CDP, confirmed disability progression; DMT, disease-modifying therapy; SPMS, secondary progressive multiple sclerosis