Effect of Siponimod on Cognition in Patients with Secondary Progressive Multiple Sclerosis (SPMS): Phase 3 EXPAND Study Subgroup Analysis

P2-051

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Background

- Cognitive impairment affects 50–70% of multiple sclerosis (MS) patients and is more severe in secondary progressive MS (SPMS) than relapsing–remitting MS[1–3]
- Decreased cognitive processing speed (CPS) constitutes a core, underlying deficit in MS patients[4–7]
- The Symbol Digit Modalities Test (SDMT) is the recommended screening text gold standard measure of CPS in MS clinical studies[5,8,9]
- A responder definition of 10% or 4-point change on SDMT has been proposed as a standard of clinically meaningful change, based on clinical changes during relapse and deteriorating employment status[5]
- Siponimod is a modulator of sphingosine-1-phosphate (S1P) receptor function with specificity for the S1P1 and S1P5 subtypes of S1P receptor[10]
- In the phase 3 EXPAND study, siponimod significantly reduced confirmed disability progression compared with placebo in SPMS patients followed for up to 3 years.11 Exploratory analyses of the EXPAND study also found that siponimod demonstrated a significant and clinically meaningful positive effect on CPS as measured by SDMT[12]

Objective

- To evaluate whether the benefit of siponimod on CPS measured using the SDMT in SPMS patients is affected by the CPS status at baseline, and with or without superimposed relapses

Methods

- SPMS patients receiving siponimod (N=1099) or placebo (N=546) in the EXPAND study underwent SDMT at baseline and at 6-monthly intervals
- Between treatment groups comparison for the change from baseline in SDMT score at Months 12 and 24, and as an average over all visits, was performed using a general linear model analysis
- Between-group comparisons for the time to a sustained improvement (increase from baseline of ≥4 points sustained on all subsequent assessments) or deterioration (decrease from baseline of ≥4 points sustained on all subsequent assessments) in SDMT score were performed on the full analysis set using a Cox proportional hazards model
- Subgroup analyses were performed for patients with or without cognitive impairment at baseline (impaired SDMT <43[13]), with baseline SDMT ≥median or <median, and with or without superimposed relapses

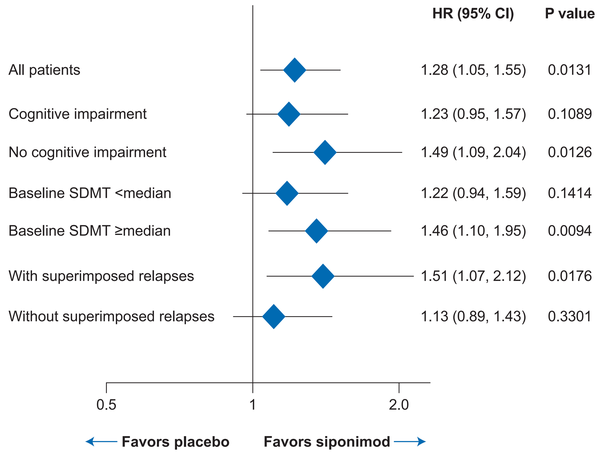
Results

- There were statistically significant differences in favour of siponimod versus placebo in change from baseline in SDMT score at Months 12 (difference 1.085 [95% confidence interval (CI) 0.227, 1.942]; p0.0132) and 24 (difference 2.303 [1.105, 3.501]; p=0.0002), and as an average over all visits (difference 1.384 [0.584, 2.183]; p=0.0007)
- The proportion of patients with sustained meaningful improvement in SDMT was significantly greater among siponimod- versus placebo-treated patients (hazard ratio [HR; 95% confidence interval (CI)] 1.28 [1.05, 1.55]; p=0.0131) (**Table 1; Figure 1**), while the proportion of patients with a sustained meaningful deterioration in SDMT was significantly less (HR [CI], 0.79 [0.65, 0.96]; p=0.0157) (**Table 2; Figure 2**)
- The proportion of patients with sustained meaningful improvement in SDMT was greater for siponimod- versus placebo-treated patients either with or without cognitive impairment at baseline, reaching statistical significance for those without pre-study impairment (HR 1.49 [1.09, 2.04]; p=0.0126) (**Table 1; Figure 1**)
- Similarly, the proportion of patients with sustained meaningful improvement was greater for siponimod- versus placebo-treated patients either with baseline SDMT ≥median or <median, achieving statistical significance for those with baseline SDMT ≥median (HR 1.46 [1.10, 1.95]; p=0.0094) (**Table 1; Figure 1**)
- The proportion of patients with sustained meaningful improvement was numerically greater for siponimod- versus placebo-treated patients with or without superimposed relapses (**Table 1; Figure 1**)

Table 1. The proportion of patients with sustained improvement in SDMT (≥4-point increase from baseline) among siponimod- versus placebo-treated patients by subgroup

Group/subgroup	Patients (N)		Proportion affected (%)		Relative risk reduction (%)
	Siponimod	Placebo	Siponimod	Placebo	
All patients	1099	546	34.9	27.0	–27.5
Cognitive impairment	618	284	39.3	31.1	–22.6
No cognitive impairment	472	257	29.1	22.6	–49.0
Baseline SDMT <median	550	252	39.6	31.1	–22.0
Baseline SDMT ≥median	540	289	30.1	23.5	–46.4
With superimposed relapses	388	202	35.1	23.8	–50.9
Without superimposed relapses	708	343	34.8	29.0	–12.6

Figure 1. Hazard ratios in patients with sustained improvement in SDMT (≥4-point increase from baseline) among siponimod- versus placebo-treated patients by subgroup

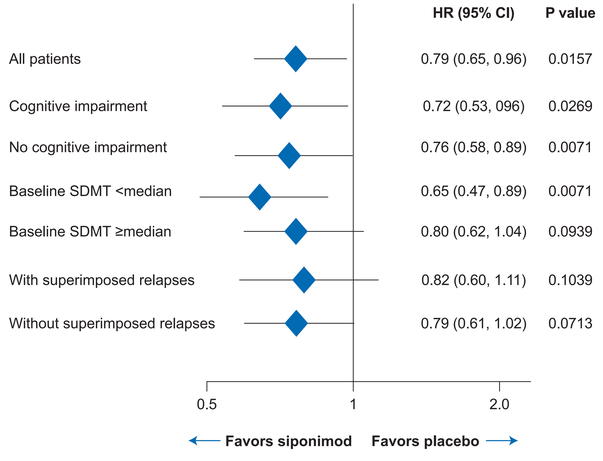


- The proportion of patients with sustained meaningful deterioration was significantly less with siponimod- versus placebo-treated patients with (HR 0.72 [0.53, 0.96]; p=0.0269) and without cognitive impairment (HR 0.76 [0.58, 1.00]; p=0.0477) (**Table 2; Figure 2**)
- Similarly, the proportion of patients with sustained meaningful deterioration was significantly less with siponimod- versus placebo-treated patients with baseline SDMT <median (HR 0.65 [0.47, 0.89]; p=0.0071), and numerically less for those with baseline SDMT ≥median (**Table 2; Figure 2**)
- The proportion of patients with sustained meaningful deterioration was less for siponimod- versus placebo-treated patients with or without superimposed relapses (**Table 2; Figure 2**)

Table 2. The proportion of patients with sustained deterioration in SDMT (≥4-point decrease from baseline) among siponimod- versus placebo-treated patients by subgroup

Group/subgroup	Patients (N)		Proportion affected (%)		Relative risk reduction (%)
	Siponimod	Placebo	Siponimod	Placebo	
All patients	1099	546	24.6	31.1	21.3
Cognitive impairment	618	284	20.9	25.8	28.4
No cognitive impairment	472	257	29.3	37.0	23.8
Baseline SDMT <median	550	252	20.1	26.3	35.0
Baseline SDMT ≥median	540	289	29.1	35.3	19.6
With superimposed relapses	388	202	28.3	37.1	18.3
Without superimposed relapses	708	343	22.5	27.5	21.3

Figure 2. Hazard ratios in patients with sustained deterioration in SDMT (≥4-point decrease from baseline) among siponimod- versus placebo-treated patients by subgroup



Conclusions

- Siponimod had a significant benefit on processing speed (as measured by SDMT), a key cognitive domain affected by MS, in patients with SPMS
- The proportion of patients with sustained improvement in SDMT was most pronounced and significantly greater among siponimod- versus placebo-treated patients in those patients with no cognitive impairment or patients with relapses
- Moreover, in patients with greater cognitive impairment, siponimod significantly reduced/prevented further deterioration versus placebo
- These findings suggest the earlier treatment is initiated the better the neuropsychological outcome

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Acknowledgments

This study was funded by Novartis Pharma AG, Basel, Switzerland. Medical writing support was provided by Ian Wright of Novartis Novartis Irl Ltd, Dublin, Ireland. The final responsibility for the content lies with the authors.

Disclosures

Ralph Benedict has received consultancy compensation from AbbVie, Biogen Idec, Novartis, Genzyme/Sanofi Aventis, Teva, Genentech, and Roche, has received grant support from Biogen Idec and Genzyme, and has served as a speaker for EMD Serono.

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

Bruce Cree has received personal compensation for consulting from AbbVie, Akili, Biogen, EMD Serono, GeNeuro and Novartis.

Patrick Vermersch has received honoraria and consulting fees from Biogen, Sanofi Genzyme, Novartis, Merck Serono, Celgene, Novartis, Roche, Servier and Almirall and research support from Biogen Idec, Sanofi Genzyme and Roche.

Gavin Giovannoni has received compensation for participating on Advisory Boards in relation to clinical trial design, trial steering committees and data and safety monitoring committees from Abbvie, Almirall, Atara Bio, Biogen, Sanofi-Genzyme, Genentech, GSK, Merck, Novartis, Roche and Teva. He is also the Co-Chief Editor of Multiple Sclerosis and Related Disorders (Elsevier).

Amit Bar-Or has received personal compensation for consulting; serving on scientific advisory boards; and/or speaking activities from Atara Biotherapeutics, Biogen Idec, Celgene/Receptos, Genentech/Roche, GlaxoSmithKline, MAPI, Medimmune, Merck/EMD Serono, Novartis and Sanofi-Genzyme.

Ralf Gold has received compensation for serving as a consultant or speaker from Bayer HealthCare, Biogen Idec, Merck Serono, Novartis and Teva Neuroscience, and 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 Kappos has received no personal compensation. Ludwig Kappos' institution (University Hospital Basel) has received in the last 3 years and used exclusively for research support: steering committee, advisory board and consultancy fees from Actelion, Bayer HealthCare, Biogen Idec, Celgene/Receptos, CSL Behring, Desitin, Genzyme, Japan Tobacco, Merck, Novartis, Pfizer, Roche, Sanofi, Santhera and Teva.

Davorka Tomic, Shannon Ritter and Göril Karlsson are employees of Novartis.

Christian Wolf is a partner at Lycalis sprl and reports compensation for his organization for consulting from Novartis, Teva, Celgene, Mylan, Synthon, BBB, ICON and Desitin; and for speaking from Mylan and Synthon.

Poster presented at the 71st Annual meeting of the American Academy of Neurology, 4–10 May 2019, Philadelphia, USA.

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