Siponimod Improves Cognitive Processing Speed in Patients With Secondary Progressive Multiple Sclerosis: EXPAND Subgroup Analyses

P22

Ralph H.B. Benedict[1], Davorka Tomic[2], Robert Fox[3], Bruce A.C. Cree[4], Patrick Vermersch[5], Gavin Giovannoni[6], Amit Bar-Or[7], Ralf Gold[8], Shannon Ritter[9], Göril Karlsson[2], Christian Wolf[10], Ludwig Kappos[11]

[1]Department of Neurology, University at Buffalo, Buffalo, NY, USA; [2]Novartis Pharma AG, Basel, Switzerland; [3]Mellen Center for Treatment and Research in Multiple Sclerosis, Neurological Institute, Cleveland Clinic, Cleveland, OH, USA; [4]UCSF Weill Institute for Neurosciences, Department of Neurology, University of California, San Francisco, CA, USA; [5]Department of Neurology, University of Lille, Lille, France; [6]Blizard Institute, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London, UK; [7]Department of Neurology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA; [8]Department of Neurology, St. Josef-Hospital/Ruhr-University Bochum, Bochum, Germany; [9]Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA; [10]Lycalis sprl, Brussels, Belgium; [11]Neurologic Clinic and Policlinic, Departments of Medicine, Clinical Research, Biomedicine and Biomedical Engineering, University Hospital and University of Basel, Basel, Switzerland

Background

- Cognitive impairment affects 50%–70% of multiple sclerosis (MS) patients and is more severe in secondary progressive MS (SPMS) than in 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 test gold standard measure of CPS in MS clinical studies[5,8,9]
- A responder definition of 10% or 4-point change on the SDMT score has been proposed as a standard of clinically meaningful change, based on clinical changes during a relapse and deteriorating employment status[5]
- Siponimod is a modulator of sphingosine-1-phosphate (S1P) receptor function with specificity for the $S1P_1$ and $S1P_5$ subtypes of the 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 the 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 mixed-model repeated measures 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 the 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 before the study

Results

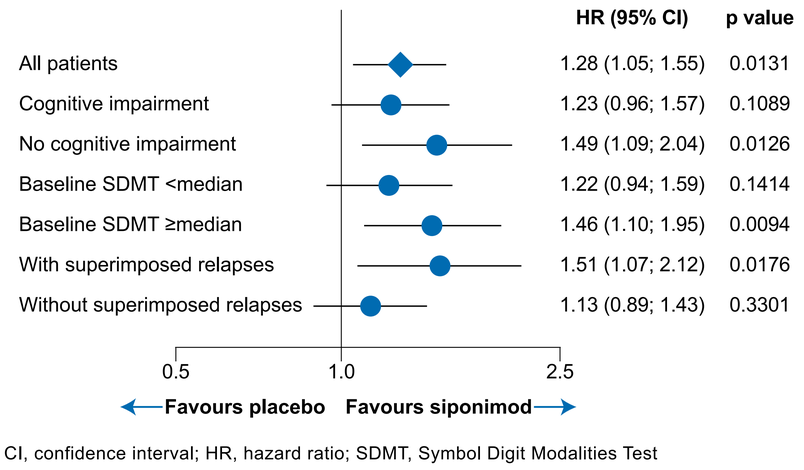
- There were statistically significant differences in favour of siponimod versus placebo in change from baseline in the SDMT score at Months 12 (difference 1.09 [95% confidence interval (CI) 0.23; 1.94]; p=0.0132) and 24 (difference 2.30 [1.11; 3.50]; p=0.0002), and as an average over all visits (difference 1.38 [0.58; 2.18]; p=0.0007)
- The proportion of patients with sustained meaningful improvement in the SDMT score was significantly greater among siponimod- versus placebo-treated patients (hazard ratio [HR] [95% 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 lower (HR [95% CI] 0.79 [0.65; 0.96]; p=0.0157) **(Table 2; Figure 2)**
- The proportion of patients with sustained meaningful improvement in the SDMT score 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 [95% CI] 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 [95% CI] 1.46 [1.10; 1.95]; p=0.0094) (**Table 1; Figure 1**)
- The proportion of patients with sustained meaningful improvement was greater for siponimod- versus placebo-treated patients either with or without superimposed relapses, achieving statistical significance for those with relapses (HR [95% CI] 1.51 [1.07; 2.12]; p=0.0176) (**Table 1; Figure 1**)
- The proportion of patients with sustained meaningful deterioration was significantly lower with siponimod- versus placebo-treated patients with (HR [95% CI] 0.72 [0.53; 0.96]; p=0.0269) and without (HR [95% CI] 0.76 [0.58; 1.00]; p=0.0477) cognitive impairment **(Table 2; Figure 2)**
- Similarly, the proportion of patients with sustained meaningful deterioration was significantly lower with siponimod- versus placebo-treated patients with baseline SDMT <median (HR [95% CI] 0.65 [0.47; 0.89]; p=0.0071) and numerically lower for those with baseline SDMT ≥median **(Table 2; Figure 2)**
- The proportion of patients with sustained meaningful deterioration was lower for siponimod- versus placebo-treated patients with or without superimposed relapses **(Table 2; Figure 2)**

Table 1. The proportion of patients with sustained improvement in the SDMT score (≥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

SDMT, Symbol Digit Modalities Test

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



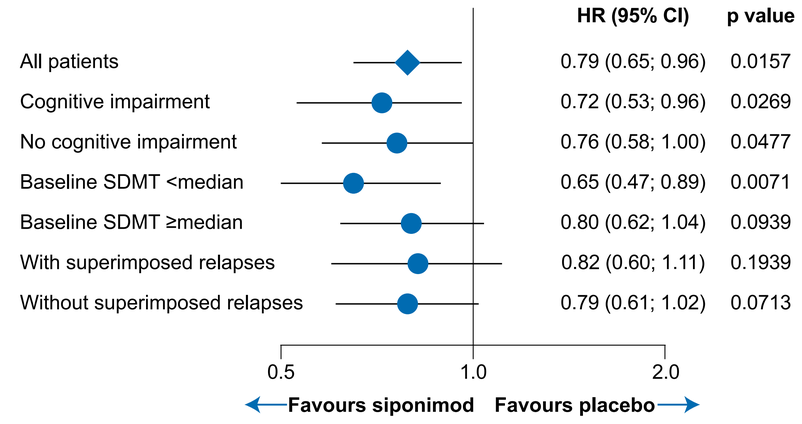
CI, confidence interval; HR, hazard ratio; SDMT, Symbol Digit Modalities Test

Table 2. The proportion of patients with sustained deterioration in the SDMT score (≥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

SDMT, Symbol Digit Modalities Test

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



CI, confidence interval; HR, hazard ratio; SDMT, Symbol Digit Modalities Test

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 the SDMT score was more pronounced and significantly greater among siponimod- versus placebo-treated patients in those with no cognitive impairment or with relapses
- Moreover, in patients with greater cognitive impairment, siponimod significantly reduced/prevented further deterioration versus placebo
- These findings suggest that the earlier treatment is initiated, the better the neuropsychological outcome

References

1. Benedict RHB, et al. *Arch Neurol.* 2006;63:1301–1306.
2. Benedict RHB, et al. *JINS.* 2017;23:832–842.
3. Planche V, et al. *Eur J Neurol.* 2016;23:282–289.
4. Forn C, et al. *J Clin Exp Neuropsychol.* 2008;30:789–796.
5. Benedict RHB, et al. *Mult Scler.* 2017;23:721–733.
6. Genova HM, et al. *J Clin Exp Neuropsychol.* 2013;35:631–641.
7. DeLuca J, et al. *J Clin Exp Neuropsychol.* 2004;26:550–562.
8. Langdon DW, et al. *Mult Scler.* 2012;18:891–898.
9. Drake AS, et al. *Mult Scler.* 2010;16:228–237.
10. Gergely P, et al. *Br J Pharmacol.* 2012;167:1035–1047.
11. Kappos L, et al. *Lancet.* 2018;391:1263–1273.
12. Benedict RHB, et al. *Eur J Neurol.* 2018;25 (suppl. 2):432[EPR2013].
13. Cohan S, et al. Presented at *AAN* 2018; S44.005.

Acknowledgements

The study was funded by Novartis Pharma AG, Basel, Switzerland. Poster layout development was supported by **Swetha Sanugomula** and **Madhavi Kanithi**, both of Novartis Healthcare Pvt. Ltd., Hyderabad, India. The final responsibility for the content lies with the authors.

Disclosures

Ralph HB 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 a 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 AC 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, 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' 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); licence fees for Neurostatus products; and grants (Bayer HealthCare, Biogen Idec, European Union, INNO-Swiss, Merck, Novartis, Roche Research Foundation, Swiss MS Society and Swiss National Research Foundation).

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

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

Poster presented at the 8th annual meeting of the International MS Cognition Society (IMSCOGS), 6–7 June 2019, Amsterdam, Netherlands.

Presenter email address: benedict@buffalo.edu

Scan to download a copy of this Poster