Does Cognitive Impairment Predict Physical Disability Progression? Evidence from EXPAND, a Phase 3 Long-Term SPMS Study

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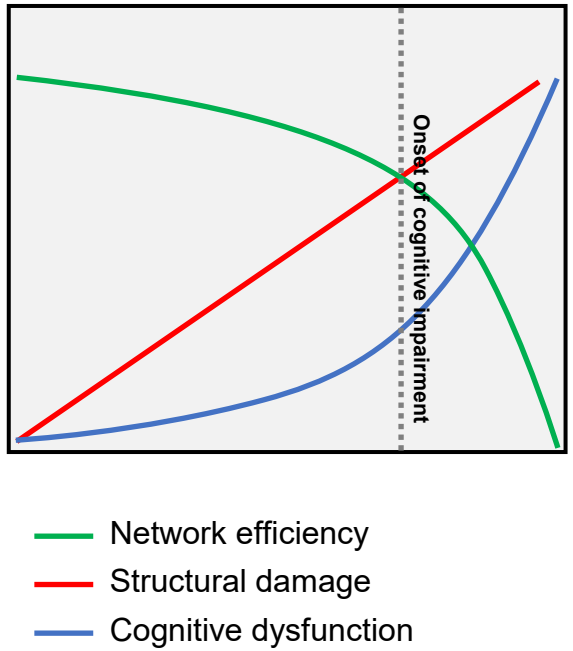
Introduction

- Cognitive impairment impacts patients' QoL and is more prevalent (up to 80%) and more severe in patients with SPMS vs those with RRMS[1,2]
- CPS may indicate functional brain reserve and network efficiency, reflecting the ability of the brain to compensate for neuro-axonal damage/loss that accumulates with disease progression[3]
  - Several smaller studies suggest that cognitive impairment/CPS in MS predicts long-term physical disability progression[4,5]
- In the Phase 3 EXPAND study in SPMS, siponimod significantly reduced the risk of disability progression and CPS worsening measured by SDMT in patients with SPMS[6,7] and the effect was sustained in the long-term[8]
- Here, we assess the association between CPS, as measured by SDMT, and physical disability progression in the EXPAND clinical trial dataset

Neuronal network dysfunction (network collapse)[9]



CPS, cognitive processing speed; MS, multiple sclerosis; QoL, quality of life; RRMS, relapsing-remitting MS; SDMT, symbol digit modalities test; SPMS, secondary progressive MS

1. Ruano L, et al. Mult Scler. 2017;23(9):1258-1267; 2. Wachowius U, et al. J Clin Exp Neuropsychol. 2005;27(1):65-77; 3. Gaetani L, et al. Neural Regen Res. 2021;16(1):36–42; 4. Moccia M, et al. Mult Scler. 2016;22(5):659-67; 5. Pitteri M, et al. Mult Scler. 2017;23(6):848-854; 6. Benedict RHB, et al. Neurology 2021;96(3):e377-e386; 7. Kappos L, et al. Lancet. 2018;391:1263–73; 8. Cree BAC. Mult Scler. 2022;In press; 9. Schoonheim MM, et al. Front Neurol. 2015;6:82.

Objectives

To assess the predictive value of cognitive processing speed (assessed by the SDMT) for physical disability progression measured by:

- Sustained deterioration to EDSS ≥7 (wheelchair dependence)
- 6-month confirmed disability progression (6mCDP) on EDSS

EDSS, expanded disability status scale; 6mCDP, 6-month confirmed disability progression; SDMT, symbol digit modalities test

Methods (1/2)

- This post hoc analysis used data from the core and extension parts of the phase 3 EXPAND study in SPMS
- Patients (1628/1651) were categorized into quartiles by baseline SDMT score and on-study (M–M24) SDMT change: worst [Q1], intermediate [Q2-Q3], and best [Q4]
- The predictive value for disability progression was assessed by comparing worst vs best quartile of baseline SDMT or on-study change (M0–24) in SDMT via Cox regression models and Kaplan-Meier analysis:

Baseline SDMT	• For baseline SDMT, the Cox regression model was adjusted for treatment, age, gender, baseline EDSS, baseline SDMT quartile and treatment-by-baseline SDMT quartile interaction
On-study change in SDMT	• For on-study change in SDMT, the Cox regression model was adjusted for treatment, age, gender, baseline EDSS, baseline SDMT and on-study change in SDMT quartile
Kaplan-Meier analysis	• Kaplan Meier curves, which are a non-parametric analysis and thus not adjusted for any covariates including baseline EDSS score were also generated for each SDMT category • Since more patients in the worst versus best baseline SDMT category had baseline EDSS=6.5 (35% versus 19%, respectively), it should be noted that the worst subset is at an increased risk of sustained deterioration to EDSS ≥7 (wheelchair dependence) in the Kaplan Meier analysis

EDSS, expanded disability status scale; M, month; MS, multiple sclerosis; Q, quartile; SDMT, symbol digit modalities test; SPMS, secondary progressive MS

Methods (2/2)

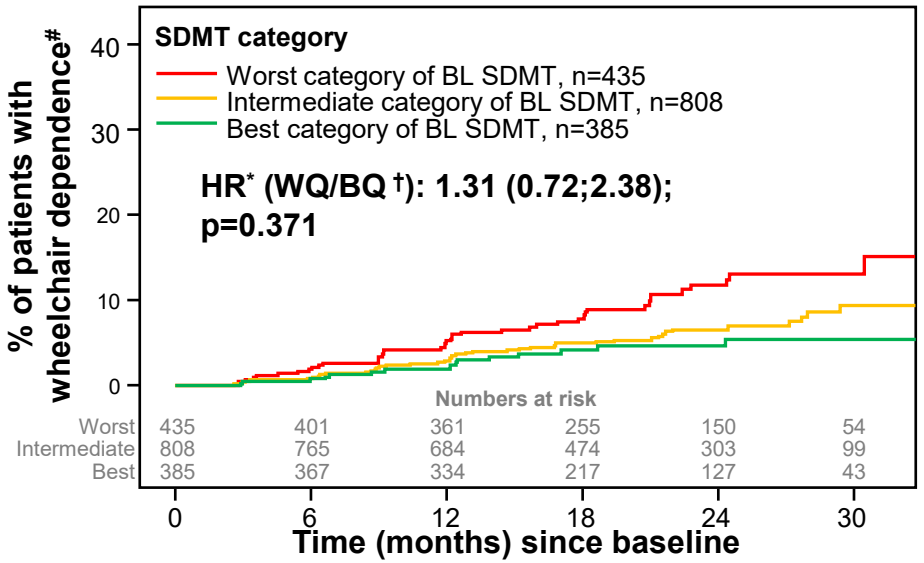
Analyses	
Core part (up to 37 months) (all patients, siponimod group and placebo group)	**Core+extension (up to 5 years)** (all patients and siponimod group)*
• Baseline SDMT as a predictor of sustained deterioration to EDSS ≥7 (wheelchair dependence) and 6mCDP	• Baseline SDMT as a predictor of sustained deterioration to EDSS ≥7 (wheelchair dependence) and 6mCDP • On-study change in SDMT (Months 0–24) as a predictor of subsequent sustained deterioration to EDSS ≥7 (wheelchair dependence) and 6mCDP

*Due to confounding, the predictive ability of CPS was not assessed in the group switching from placebo to siponimod in the extension

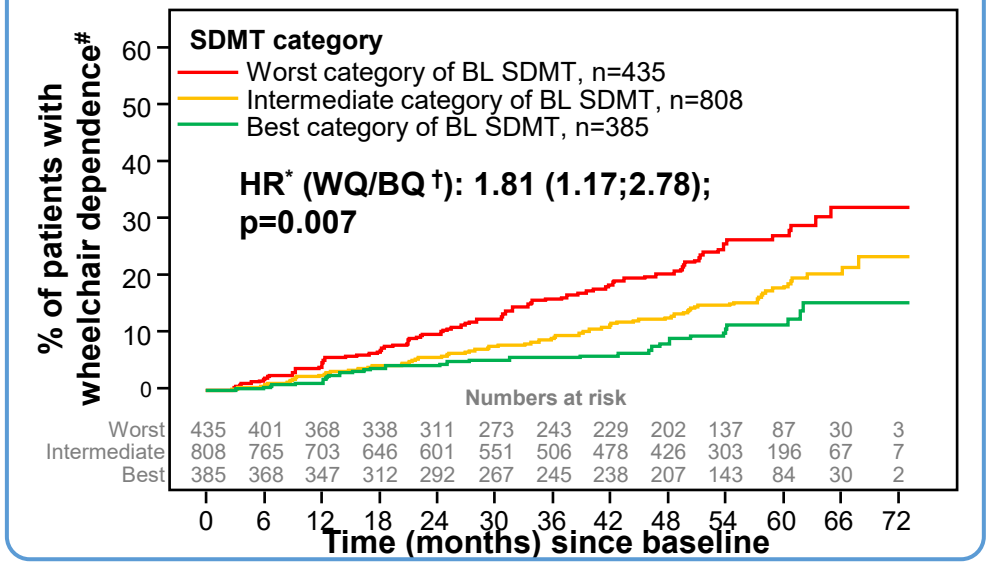
Abbreviations: EDSS, expanded disability status scale; SDMT, symbol digit modalities test; 6mCDP, 6-month confirmed disability progression

Results: Predictive value of baseline SDMT for reaching wheelchair dependency (all patients)

Core part



Core+extension part

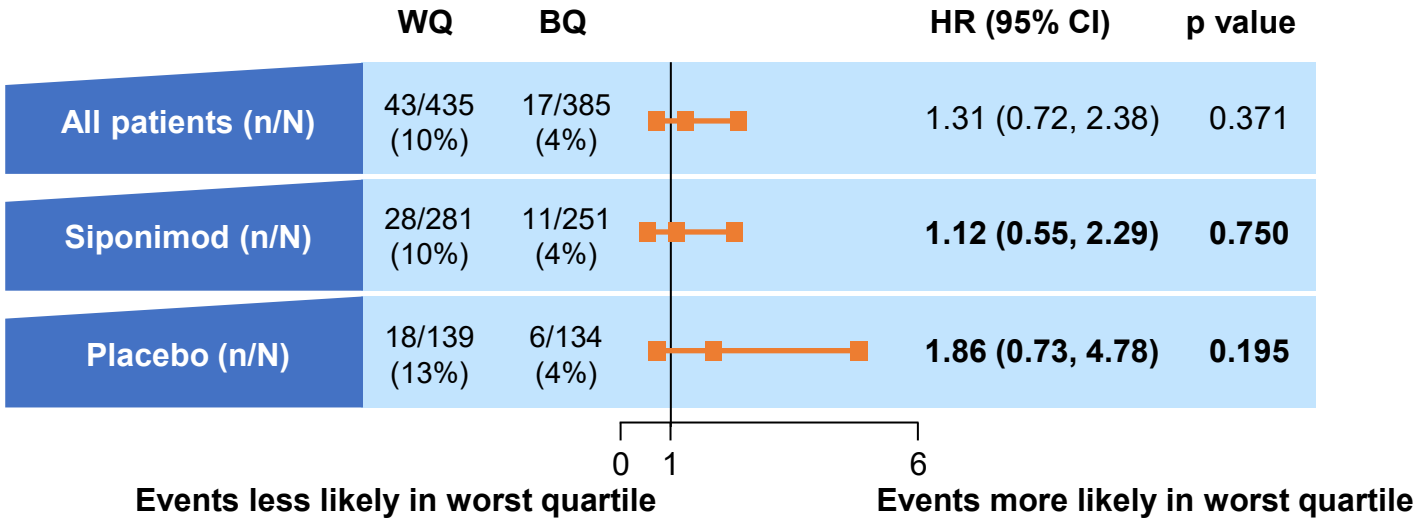


- **In the core part, patients in the worst quartile of SDMT at baseline were at a numerically higher risk of reaching sustained deterioration to EDSS ≥7 (wheelchair dependence) vs patients in the best quartile of SDMT**
- **The predictive value of baseline SDMT increased with long-term follow-up**
  - **There was an almost 2-fold increased risk of wheelchair dependence [WQ/BQ] in the core+extension part**

*Adjusted for baseline EDSS and other confounders; †WQ of BL SDMT score ≤29 (minimum 0); BQ of BL SDMT score ≥49 (maximum 83); #EDSS ≥7
BL, baseline; BQ, best quartile; CPS, cognitive processing speed; EDSS, expanded disability status scale; SDMT, symbol digit modalities test; WQ, worst quartile

Results: Short-term predictive value for disability progression of baseline SDMT (core part) by treatment arm

Wheelchair dependency (sustained EDSS ≥7)

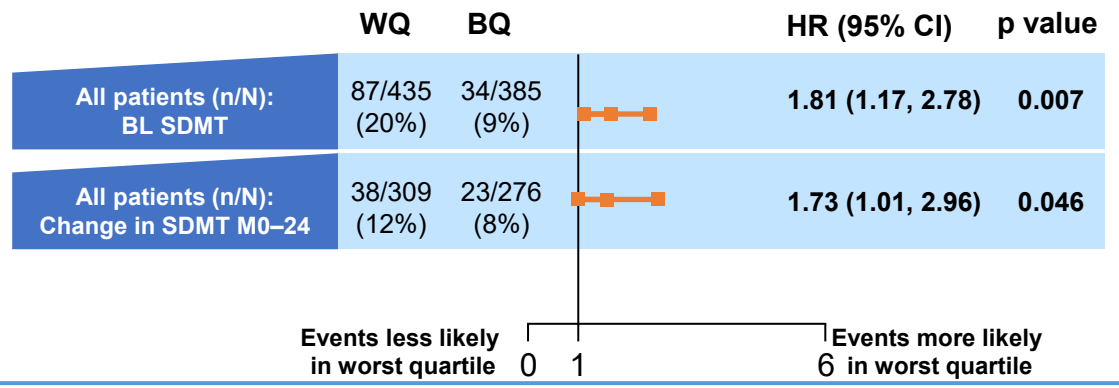


- **The short-term predictive value of baseline SDMT for reaching sustained EDSS ≥7 was more obvious in the placebo arm ($HR_{WQ/BQ}$=1.86) vs the siponimod arm ($HR_{WQ/BQ}$=1.12) likely due to the treatment effect of siponimod preventing relatively more events in the WQ and hence reducing the risk of wheelchair dependency**
- **No significant predictive value for 6mCDP was observed**

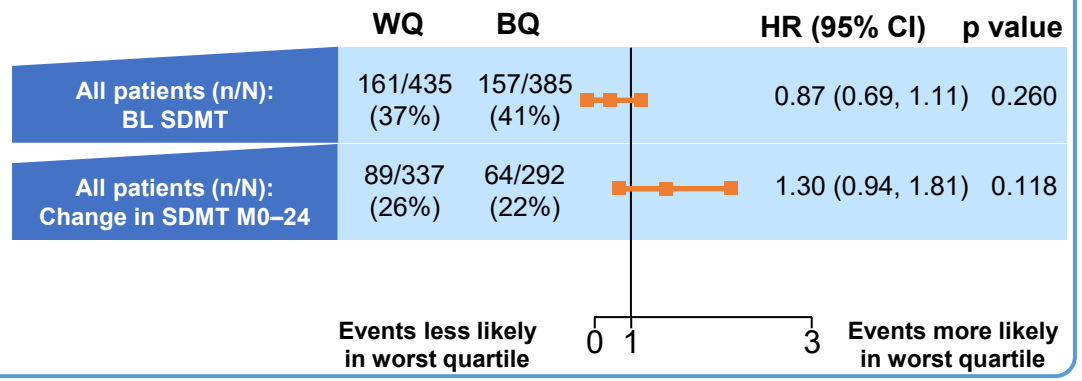
n=number of patients with event, N=number of patients included in the analysis
BQ, best quartile; EDSS, expanded disability status scale; HR, hazard ratio; MS, multiple sclerosis; SDMT, symbol digit modalities test; SPMS, secondary progressive MS; WQ, worst quartile; 6mCDP, 6-month confirmed disease progression

Results: Long-term predictive value for disability progression of baseline SDMT and on-study SDMT change (core+extension part)

Wheelchair dependency (sustained EDSS ≥7)



6-month confirmed disease progression



- **Baseline SDMT and on-study change in SDMT were predictive of wheelchair dependency in the long-term**
- **No significant predictive value of 6mCDP was observed**

n=number of patients with event, N=number of patients included in the analysis
BL, baseline; BQ, best quartile; HR, hazard ratio; MS, multiple sclerosis; SDMT, symbol digit modalities test; WQ, worst quartile; 6mCDP, 6-month confirmed disease progression

Conclusions

- Both baseline and on-study worsening in CPS (measured by the SDMT), were predictive of physical disability progression over the longer term (up to 5 years) in patients with SPMS as indicated by the significant association with the outcome of reaching the milestone of wheelchair dependency (sustained EDSS ≥7)
- In line with previous smaller studies in MS, our results support the value of CPS as an indirect measure of network efficiency and functional brain reserve that could predict future disease progression
- Furthermore, the results support the relevance of CPS monitoring in daily practice to help identify patients at risk of progression and help uncover ‘silent’ signs of progression
- Finally, these findings change our world view of MS away from simply a physically disabling disease to include cognition as a key component to measure and address

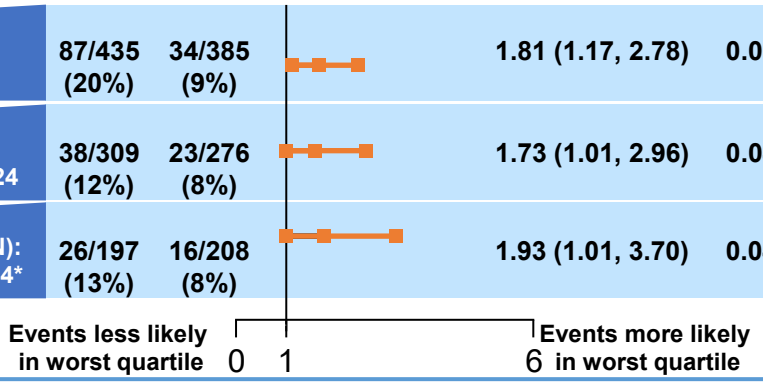
CPS, cognitive processing speed; EDSS, expanded disability status scale; MS, multiple sclerosis; SDMT, symbol digit modalities test

Back-up slide

Results: Long-term predictive value for disability progression of baseline SDMT and on-study SDMT change (core+extension part)

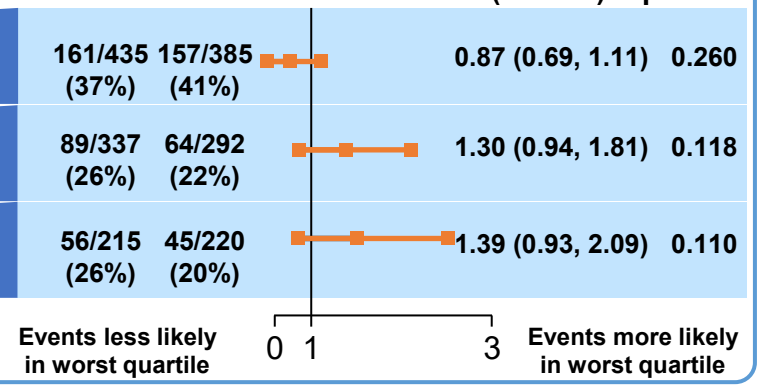
Wheelchair dependency (sustained EDSS ≥7)

	WQ	BQ	HR (95% CI)	p value
All patients (n/N): BL SDMT	87/435 (20%)	34/385 (9%)	1.81 (1.17, 2.78)	0.007
All patients (n/N): Change in SDMT M0–24	38/309 (12%)	23/276 (8%)	1.73 (1.01, 2.96)	0.046
Siponimod group* (n/N): Change in SDMT M0–24*	26/197 (13%)	16/208 (8%)	1.93 (1.01, 3.70)	0.047



6-month confirmed disease progression

	WQ	BQ	HR (95% CI)	p value
All patients (n/N): BL SDMT	161/435 (37%)	157/385 (41%)	0.87 (0.69, 1.11)	0.260
All patients (n/N): Change in SDMT M0–24	89/337 (26%)	64/292 (22%)	1.30 (0.94, 1.81)	0.118
Siponimod group* (n/N): Change in SDMT M0–24*	56/215 (26%)	45/220 (20%)	1.39 (0.93, 2.09)	0.110



*The siponimod group refers for patients who received siponimod in the core and the open-label extension part of the EXPAND study

- **Baseline SDMT and on-study change in SDMT were predictive of wheelchair dependency in the long-term, but not predictive of 6mCDP**

n=number of patients with event, N=number of patients included in the analysis
BL, baseline; BQ, best quartile; HR, hazard ratio; MS, multiple sclerosis; SDMT, symbol digit modalities test; SPMS, secondary progressive MS; WQ, worst quartile; 6mCDP, 6-month confirmed disease progression